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0 325 397
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EUROPEAN PATENT APPLICATION

⑬ Application number: 89300380.6

⑭ Date of filing: 17.01.89

⑮ Int. Cl.4: C 07 C 127/19
C 07 C 127/17,
C 07 C 157/09,
C 07 C 157/07,
C 07 C 87/455, A 61 K 31/17

⑯ Priority: 20.01.88 JP 10098/88
19.07.88 JP 180119/88

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⑲ Designated Contracting States:
AT BE CH DE ES FR GB GR IT LI LU NL SE

⑳ Applicant: YAMANOUCHI PHARMACEUTICAL CO. LTD.
No. 3-11 Nihonbashi-Honcho, 2-chome Chuo-ku
Tokyo (JP)

㉑ Inventor: Ito, Noriki
Angel Helm 2-503 614 Ohmagi
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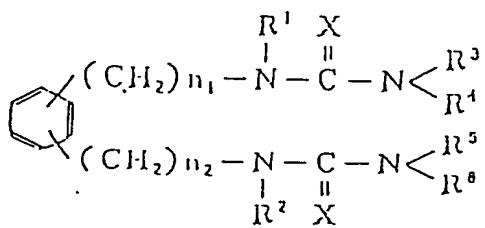
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㉓ Diurea derivatives useful as medicaments and processes for the preparation thereof.

㉔ Diurea Derivatives represented by the following general formula and salts thereof:



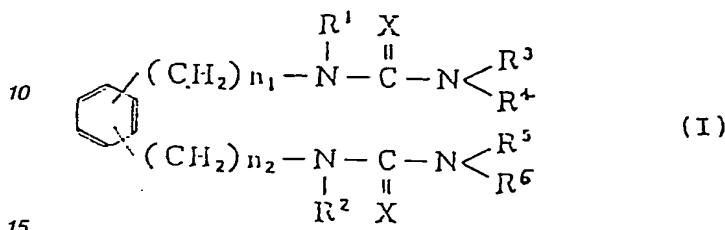
The above compounds inhibit acyl-coenzyme A cholesterol acyl-transferase (ACAT enzyme), and thereby control the accumulation of cholesterol ester on the smooth muscle of arterial walls.

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Description**Diurea Derivatives useful as medicaments and processes for the preparation thereof.**

The present invention relates to diurea derivatives of formula (I) (and salts thereof) useful as medicaments and to their preparation

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wherein

R¹ and R² are the same or different and selected from alkyl groups, cycloalkyl groups and lower alkyl groups substituted by cycloalkyl radical(s);

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R³, R⁴, R⁵ and R⁶ are the same or different and selected from a hydrogen atom and lower alkyl, cycloalkyl, aralkyl, pyridyl and phenyl groups (any phenyl group optionally having one or more substituents, e.g. selected from halogen atoms and lower alkyl, halogen-substituted lower alkyl, nitro, amino, mono- and di-lower alkylamino, lower acylamino, hydroxyl, lower alkoxy and lower acyloxy radicals);

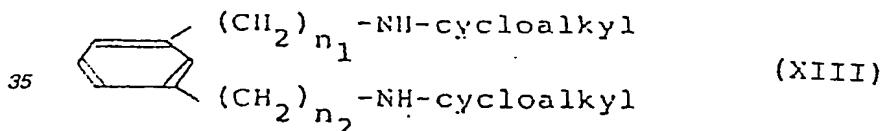
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X represents an oxygen or sulfur atom; and n₁ and n₂ are the same or different integers of 1 to 6.

Preferred compounds according to the invention include those wherein R¹ and R² are cycloalkyl groups; R³ and R⁵ are the same or different phenyl groups; R⁴ and R⁶ are the same or different and selected from a hydrogen atom and C₁-C₅ alkyl, cycloalkyl, aralkyl, pyridyl, and phenyl groups; n₁ and n₂ are integers of 1 to 3.

The invention also provides intermediate compounds of the following formula :

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40 wherein n₁ and n₂ are the same or different integers of 1 to 6.

It is known that deposition of cholesterol in the vascular system is an etiological cause of various diseases including coronary heart diseases. Atheromatous arteriosclerosis is a form of arteriosclerosis characterized by the accumulation and hypertrophication of lipid, particularly cholesterol ester, on the medium and large arterial wall.

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Recently, it has been found that acyl-coenzyme A cholesterol acyl-transferase (ACAT) catalyzes the formation of cholesterol ester. Thus, the excessive accumulation of cholesterol ester on the arterial wall is connected with increase of ACAT enzyme. Accordingly, inhibiting ACAT enzyme should decrease cholesterol esterification rate and control the formation and development of atheromatous disorder.

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Cholesterols in foodstuffs are absorbed as free cholesterol, esterified by the action of ACAT enzyme, and then released into the blood in the form of chylomicron. Therefore, inhibiting ACAT enzyme should control absorption of cholesterol from foodstuffs into the intestine and re-absorption of cholesterol released into the intestine.

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We have found the formula (I) compounds and their salts, which inhibit ACAT enzyme and hence can reduce the deposition of cholesterol on the arterial wall and control the absorption of cholesterol into the intestine. Compounds disclosed in U.S. -A-4,387,105 have been known as ACAT enzyme inhibitors, but are structurally different from formula (I).

Diruea compounds with the urea radical connected to phenyl via alkylene are disclosed in Japanese Patent Publication Nos. (Sho) 46-41462 and 47-29576, but these compounds are described as stabilizing agents for polyolefines and antideteriorating agents for rubber, and they are not of formula (I).

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Herein, "cycloalkyl" is cyclic alkyl, preferably of 3 to 18 carbon atoms, and examples include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclononyl, cyclodecyl, cyclododecyl, cyclotridecyl, cyclopentadecyl and the like; cyclo-alkyls having 6 to 10 carbon atoms are most preferable. "Lower alkyl" is straight or branched alkyl having 1 to 5 carbon atoms, and examples include methyl, ethyl, propyl, isopropyl,

butyl, isobutyl, sec.-butyl, tert.-butyl, pentyl (amyl), isopentyl, tert.-pentyl, neopentyl, 1-methylbutyl, 2-methylbutyl, 1,2-dimethylpropyl and the like. A "lower alkyl substituted by cycloalkyl" means lower alkyl, any position of which is substituted by cycloalkyl, and examples include cyclopropyl-methyl, 2-cyclobutylethyl, cyclopentylmethyl, 2-cyclopentylethyl, 1-cyclopentylethyl, cyclohexylmethyl, 1-cyclohexylethyl, 2-cyclohexylethyl, 1-cyclohexylpropyl, 2-cyclohexylpropyl, 3-cyclohexylpropyl, 1-cyclohexylbutyl, 2-cyclohexylbutyl, 3-cyclohexylbutyl, 4-cyclohexylbutyl, cycloheptylmethyl, 2-cycloheptylethyl, 3-cycloheptylpropyl, 4-cycloheptylbutyl, 5-cycloheptylpentyl, cyclooctylmethyl, 2-cyclooctylethyl, 3-cyclooctylpropyl, 4-cyclooctylbutyl, cyclononylmethyl, cyclodecylmethyl, cyclododecylmethyl, cyclotridecylmethyl, 2-cyclotridecylethyl, cyclo-tetradecylmethyl, cyclopentadecylmethyl and the like.

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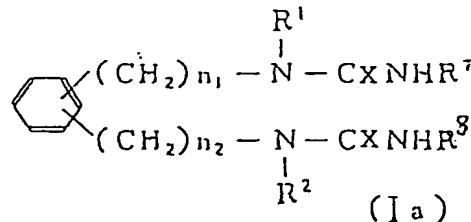
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Halogen atom includes fluorine, chlorine, bromine and iodine. Lower alkyl substituted by halogen atom means lower alkyl, any position of which is substituted by halogen, and examples include trichloromethyl, trifluoromethyl, 2,2,2-trichloroethyl, 2,2,2-trifluoroethyl, 2,2,2-tribromoethyl and the like. Mono- and di-lower alkylamino means amino substituted by one or two lower alkyls and examples include methylamino, ethylamino, propylamino, dimethylamino, diethylamino and the like. Lower acylamino means amino substituted by acyl having 1 to 5 carbon atoms, and examples thereof include formylamino, acetylamino, propionylamino and butyrylamino. Lower alkoxy includes methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec.-butoxy, tert.-butoxy, pentyloxy (amyloxy), isopentyloxy, tert.-pentyloxy, neopentyloxy, 2-methylbutoxy, 1,2-dimethylpropoxy, 1-ethylpropoxy and the like. Lower acyloxy means acyloxy having 2 to 5 carbon atoms, and examples include acetoxy, propionyloxy butyloxy, and the like. When a phenyl has two or more substituents they may be the same or different.

Compounds of formula (I) form salts, including acid addition salts with mineral acids such as hydrochloric, hydrobromic, hydroiodic, sulfuric, nitric and phosphoric acids etc., and with organic acids such as formic, acetic, oxalic, citric, succinic, fumaric, maleic, malic, tartaric, methanesulfonic, and ethanesulfonic acids etc.

Compounds according to the present invention may be prepared by various methods, e.g. :

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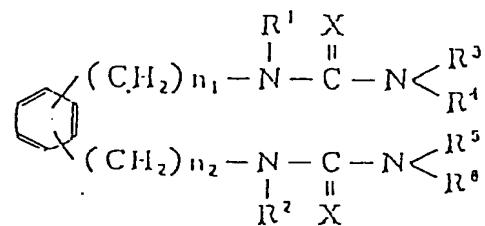
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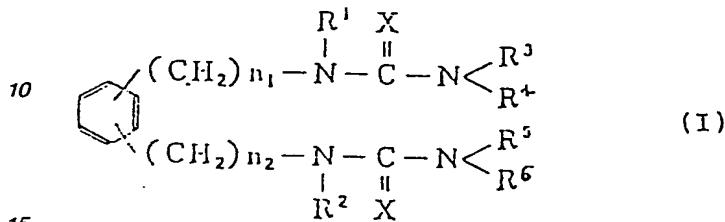
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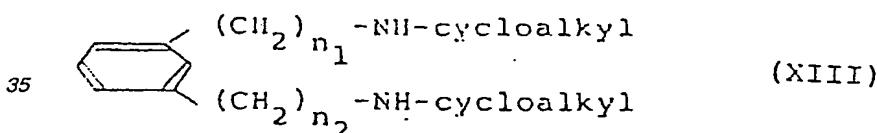
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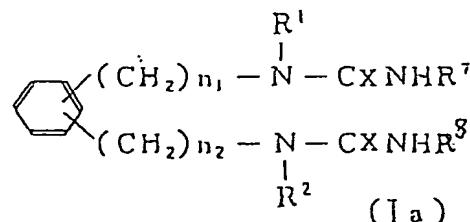
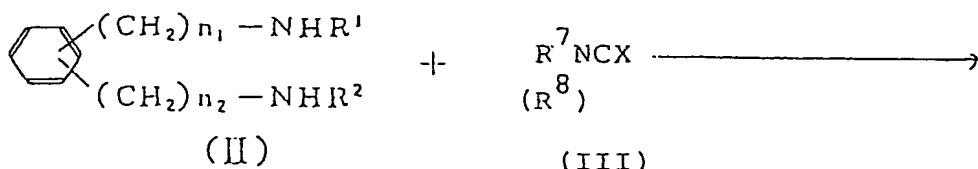
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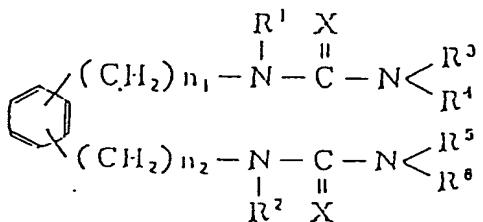
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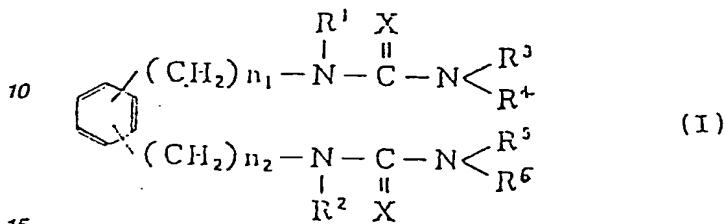
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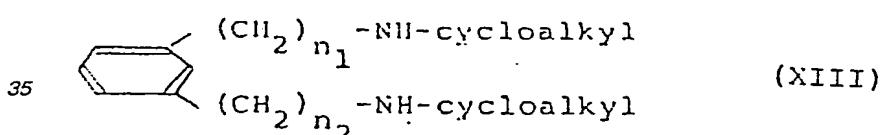
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60 Herein, "cycloalkyl" is cyclic alkyl, preferably of 3 to 18 carbon atoms, and examples include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclononyl, cyclodecyl, cyclododecyl, cyclotridecyl, cyclopentadecyl and the like; cyclo-alkyls having 6 to 10 carbon atoms are most preferable. "Lower alkyl" is straight or branched alkyl having 1 to 5 carbon atoms, and examples include methyl, ethyl, propyl, isopropyl,

butyl, isobutyl, sec.-butyl, tert.-butyl, pentyl (amyl), isopentyl, tert.-pentyl, neopentyl, 1-methylbutyl, 2-methylbutyl, 1,2-dimethylpropyl and the like. A "lower alkyl substituted by cycloalkyl" means lower alkyl, any position of which is substituted by cycloalkyl, and examples include cyclopropyl-methyl, 2-cyclobutyl-ethyl, cyclopentylmethyl, 2-cyclopentylethyl, 1-cyclopentylethyl, cyclohexylmethyl, 1-cyclohexylethyl, 2-cyclohexylethyl, 1-cyclohexylpropyl, 2-cyclohexylpropyl, 3-cyclohexylpropyl, 1-cyclohexylbutyl, 2-cyclohexylbutyl, 3-cyclohexylbutyl, 4-cyclohexylbutyl, cycloheptylmethyl, 2-cycloheptylethyl, 3-cycloheptylpropyl, 4-cycloheptylbutyl, 5-cycloheptylpentyl, cyclooctylmethyl, 2-cyclooctylethyl, 3-cyclooctylpropyl, 4-cyclooctylbutyl, cyclononylmethyl, cyclodecylmethyl, cyclododecylmethyl, cyclotridecylmethyl, 2-cyclotridecylethyl, cyclo-tetradecylmethyl, cyclopentadecylmethyl and the like.

The "alkyl" groups preferably have 1 to 10 carbon atoms, and in addition to the specific examples of lower alkyl, examples include straight or branched alkyl such as hexyl, isoheyl, 1-methylpentyl, 2-methylpentyl, 3-methylpentyl, 1,1-dimethylbutyl, 1,2-dimethylbutyl, 1,3-dimethylbutyl, 2,2-dimethylbutyl, 2,3-dimethylbutyl, 1-ethylbutyl, 1,1,2-trimethylpropyl, 1-ethyl-1-methylpropyl, heptyl, 1-methylhexyl, 2-methylhexyl, 3-methylhexyl, 4-methylhexyl, 5-methylhexyl, 1,1-dimethylpentyl, 1,2-dimethylpentyl, 1,3-dimethylpentyl, 1,4-dimethylpentyl, 2,2-dimethylpentyl, 2,3-dimethylpentyl, 2,4-dimethylpentyl, 3,3-dimethylpentyl, 3,4-dimethylpentyl, 1-ethylpentyl, 2-ethylpentyl, 3-ethylpentyl, 1,1,2-trimethylbutyl, 1,1,3-trimethylbutyl, 1,2,2-trimethylbutyl, 2,2,3-trimethylbutyl, 1-ethyl-1-methylbutyl, 1-ethyl-2-methylbutyl, 1-ethyl-3-methylbutyl, 1-propylbutyl, 1-isopropylbutyl, octyl, 6-methylheptyl, nonyl, 7-methylocetyl, decyl, 8-methylnonyl and the like.

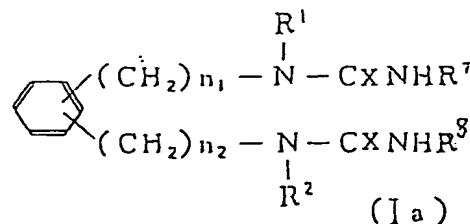
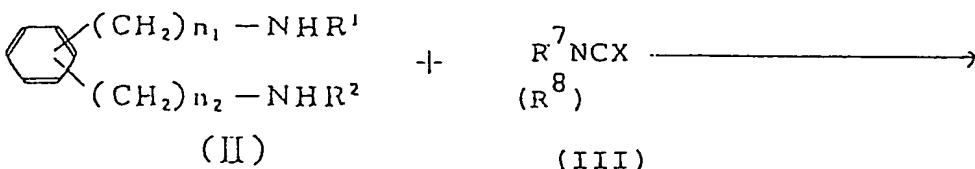
The "aralkyl" groups are alkyls (e.g. of 1 to 10 carbon atoms) substituted by aryl - e.g. phenyl, naphthyl, pyridyl, and the like. Representative examples include benzyl, phenethyl, phenylpropyl, phenylbutyl, phenylpentyl, phenylhexyl, naphthylmethyl, pyridylmethyl, pyridylethyl and the like. "Pyridyl" includes 2-, 3- and 4-pyridyl radicals. In addition, phenyl radicals may be substituted, e.g. by one or more groups selected from lower alkyl, halogen-substituted lower alkyl, nitro, amino, mono- and di-lower alkylamino, lower acylamino, hydroxyl, lower alkoxy and lower acyloxy radicals and halogen atoms.

Halogen atom includes fluorine, chlorine, bromine and iodine. Lower alkyl substituted by halogen atom means lower alkyl, any position of which is substituted by halogen, and examples include trichloromethyl, trifluoromethyl, 2,2,2-trichloroethyl, 2,2,2-trifluoroethyl, 2,2,2-tribromoethyl and the like. Mono- and di-lower alkylamino means amino substituted by one or two lower alkyls and examples include methylamino, ethylamino, propylamino, dimethylamino, diethylamino and the like. Lower acylamino means amino substituted by acyl having 1 to 5 carbon atoms, and examples thereof include formylamino, acetylamino, propionylamino and butyrylamino. Lower alkoxy includes methoxy, ethoxy, propoxy, isoproxy, butoxy, isobutoxy, sec.-butoxy, tert.-butoxy, pentyloxy (amyloxy), isopentyloxy, tert.-pentyloxy, neopentyloxy, 2-methylbutoxy, 1,2-dimethylpropoxy, 1-ethylpropoxy and the like. Lower acyloxy means acyloxy having 2 to 5 carbon atoms, and examples include acetoxy, propionyloxy butyloxy, and the like. When a phenyl has two or more substituents they may be the same or different.

Compounds of formula (I) form salts, including acid addition salts with mineral acids such as hydrochloric, hydrobromic, hydroiodic, sulfuric, nitric and phosphoric acids etc., and with organic acids such as formic, acetic, oxalic, citric, succinic, fumaric, maleic, malic, tartaric, methanesulfonic, and ethanesulfonic acids etc.

Compounds according to the present invention may be prepared by various methods, e.g. :

Process 1

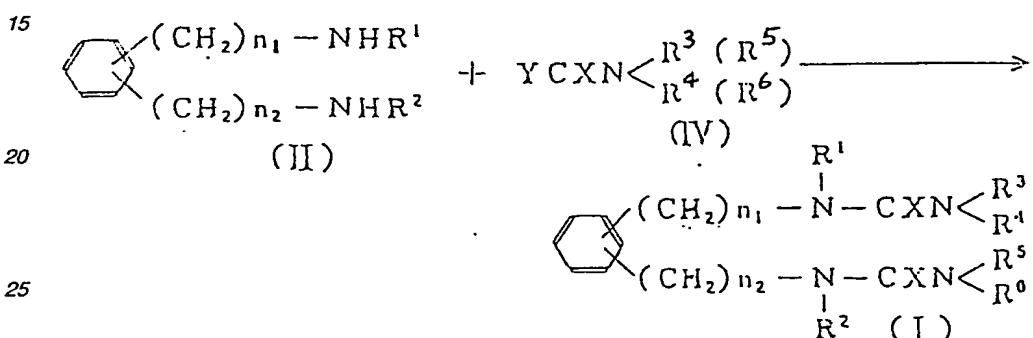


wherein

R⁷ and R⁸ are the same or different and selected from a hydrogen atom and cycloalkyl, aralkyl, pyridyl and phenyl groups (where phenyl may be substituted e.g. by one or more of lower alkyl, halogen, nitro, amino, mono- and di-lower alkylamino, lower acylamino, hydroxyl, lower alkoxy and lower acyloxy); and R¹, R², X, n₁ and n₂ are as previously defined.

5 Compounds of formula (Ia) may be obtained by reacting diamino compound (II) with one or more isocyanate compounds (III). Isocyanate compound (III) may be used in an amount of 2 or more moles per mole of compound (II). The reaction may be carried out in an inert solvent, such as N,N-dimethylformamide, pyridine, benzene, toluene, dioxane, tetrahydrofuran, ether, chloroform, dichloromethane, dichloroethane, n-hexane etc. at room temperature or with heating.

10 Process 2

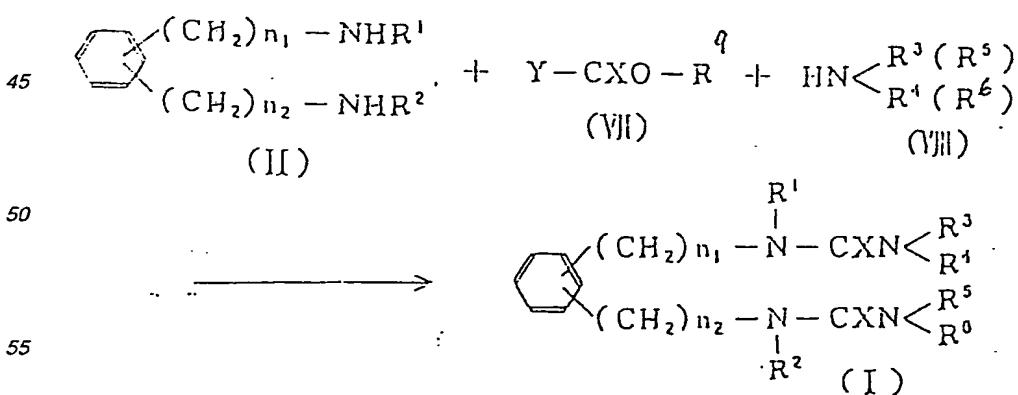


30 wherein

Y represents a halogen atom, and R¹, R², R³, R⁴, R⁵, R⁶, X, n₁ and n₂ are as defined above.

Compounds of formula (I) may be prepared by reacting amino compound (II) with halogen compound(s) (IV). The reaction may be carried out by reacting amino compound (II) with 2 or more moles of halogen compound (IV) in an inert solvent, such as N,N-dimethylformamide, benzene, toluene, dioxane, tetrahydrofuran, ether, chloroform, dichloromethane, dichloroethane, n-hexane etc. The reaction temperature may be suitably controlled according to the kind of starting compound and the solvent, but may be conventionally set at room temperature or above.

40 Process 3



60 wherein

R¹, R², R³, R⁴, R⁵, R⁶, X, Y, n₁ and n₂ are as defined above, and R⁹ represents a lower alkyl or phenyl group.

Compounds of formula (I) may be obtained by reacting amino compound(s) (VIII) with carbon halide compound (VII) to give carbamic acid ester, and then reacting the resulting compound with compound (II).

Examples of carbon halide compound

(VII) include isobutylcarbon chloride, methylcarbon chloride, ethylcarbon bromide, phenylcarbon chloride, and the like. In addition, in order to promote the reaction, it is advantageous to effect the reaction in the presence of base such as potassium carbonate, sodium carbonate, sodium hydroxyde, potassium hydroxide, triethylamine, N,N-dimethylaniline and the like. Suitable reaction solvents include inert solvents such as N,N-dimethylformamide, chloroform, benzene, toluene, xylene, dioxane, ether, tetrahydrofuran, chloroform, dichloromethane, dichloroethane and the like. When amino compound (II) is reacted with carbon halide compound, the reaction temperature may be set below or at room temperature, whereas the temperature for the reaction between carbamic acid ester thus obtained and compound (II) may be set above or at room temperature.

Other methods for preparing the desired compounds include converting one substituent into another. Thus among the substituents of a phenyl radical, one may replace an amino radical with a mono- or di-alkylamino or acylamino radical, a nitro radical with an amino radical, or an acyloxy radical with a hydroxyl radical.

To replace aromatic amino with aromatic (mono- or di-) alkylamino, although conventional alkylation can be employed, reductive amination is preferable, in which the resulting compound is reacted with aldehyde to give imine, which is then reduced to amine.

For the reduction of imine, it is preferable to employ a catalyst such as palladium-carbon, platinum oxide and the like, or metal hydride such as sodium cyanoborohydride, lithium cyanoborohydride and the like.

For the replacement of aromatic nitro with aromatic amino, conventional catalytic reduction may be employed. Palladium-carbon, Raneynickel, platinum and the like are used as catalysts.

Aromatic amino may be replaced by acylamino by conventional acylation, wherein active derivative such as anhydride, halide, mixed acid anhydride of lower alkyl carboxylic acid are used.

Substitution of acyloxy by hydroxy may be readily effected by using a base (for example, sodium hydroxide, potassium hydroxide, sodium carbonate and the like). Diamino compound (II) used as a starting compound in the present invention may be prepared as follows:

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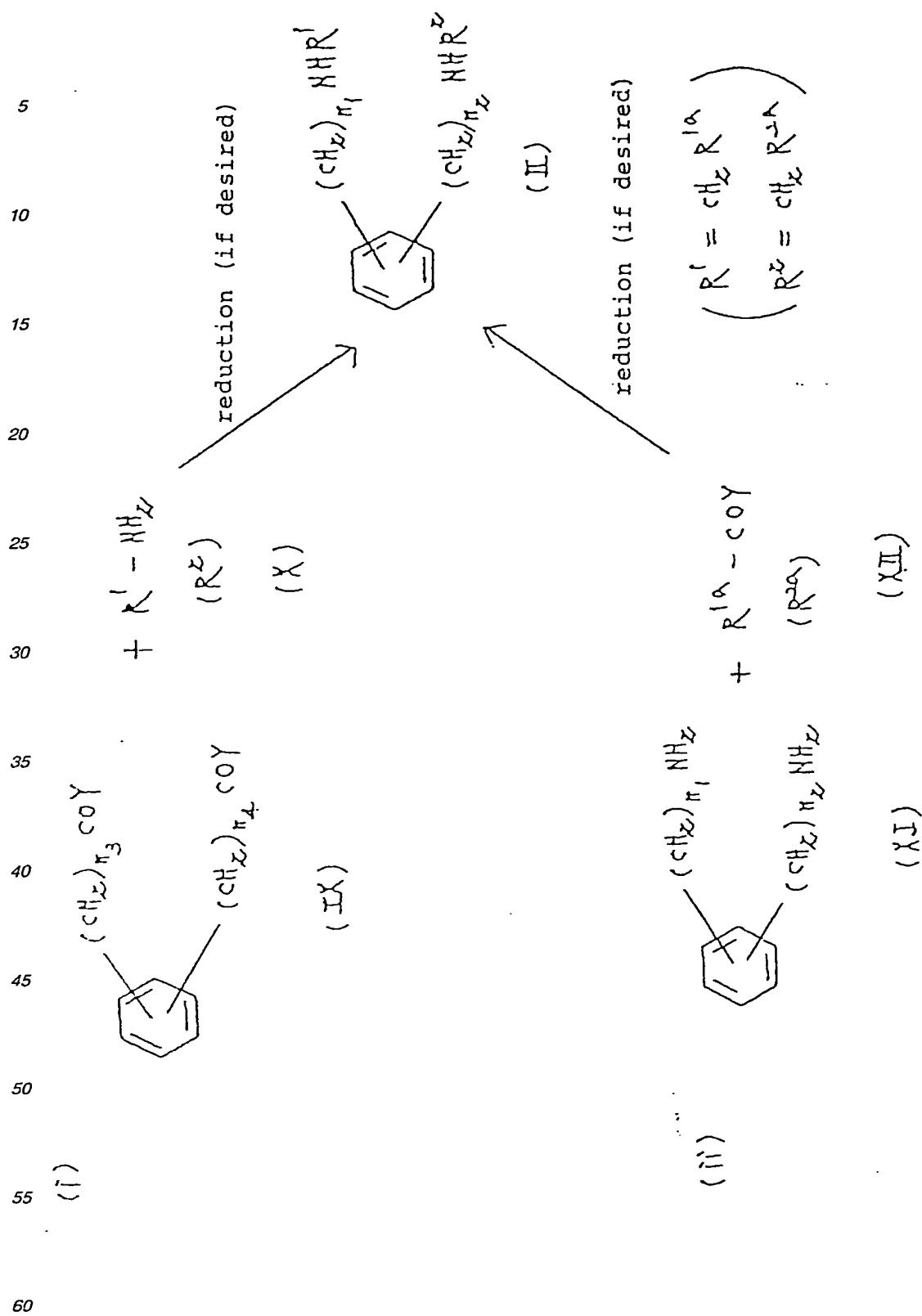
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65 wherein

Y is a hydrogen or halogen atom, n₃ and n₄ are the same or different and selected from 0 and integers of 1 to 5, and n₁, n₂, R¹ and R² are as defined above. Phenylenediamine derivative (II_a) may be obtained (i) by reacting carbonyl compound (IX) with amino compound (X) and then, if desired, reducing or (ii) by reacting diamine compound (XI) with carbonyl compound (XII) and then, if desired, reducing.

The temperature for reaction of compounds (IX) and (X), or of compounds (XI) and (XII) may be set under ice-cooling or at room temperature. Benzene, hexane, toluene, xylene, dichloromethane, chloroform, N,N-dimethylformamide and the like may be used as reaction solvent.

To accelerate the reaction, it is preferable to add organic base such as trimethylamine, triethylamine or the like or inorganic base such as sodium carbonate, sodium hydrogen carbonate or the like.

The reduction may be effected using aluminium lithium hydride, diisobutylaluminium hydride, bis(2-methoxyethoxy) aluminium sodium hydride, tetrahydrofuran-borate complex, dimethylsulfide-borate complex or the like, in a solvent such as toluene, benzene, xylene, tetrahydrofuran, dioxane, ether, etc. The reaction may be conducted under heating or ice-cooling or at room temperature. The compound (I) or (II) of the present invention thus obtained may be separated and purified in free form or salt form by salt-forming or de-salting by conventional methods and extraction, crystallization, chromatography, etc. The compounds of formula (I) and their salts inhibit ACAT enzyme, and thereby control the accumulation of cholesterol ester on the smooth muscle of arterial walls.

Compared with known anti-lipidemia agents, the present compounds control the absorption of cholesterol into the intestine and accelerate catabolic excretion of cholesterol in the liver, and thereby lower the cholesterol level in blood. The present compounds reduce the accumulation and storage of cholesterol on the arterial wall, and thereby control the formation or development of atheromatous arteriosclerosis.

As can be seen from animal tests, compounds (I) and their salts lower total cholesterol and low density lipoprotein (LDL) in blood; they thus lower lipid level in blood and are useful for prevention and treatment of various diseases related to arteriosclerosis such as cerebral infarction, temporary ischemic spasm, angina pectoris, peripheral thrombus and ileus.

Effects of the present compounds are verified as follows:

(i) ACAT enzyme inhibiting activity

Inhibiting activity against acyl CoA : cholesterol acyltransferase (ACAT) activity of rabbit's liver microsome According to Heider's method [J.G. Heider et al., J. of Lipid Res. Vol. 24, 1127-34 (1983)], rabbit's liver microsome was treated to obtain an enzyme fraction.

To 0.154M of phosphoric acid buffer solution (pH 7.4), 2mM of dithiothreitol, 36μM of bovine serum albumin and 10 to 100μg of microsome fraction, liposome prepared by Suckling's method [K.E. Suckling et al., FEBS Letters, Vol. 151, No. 1, 111-116 (1983)] was added to give 20% v/v. To this, 2% v/v of dimethylsulfoxide solution of each concentration of compound to be tested was added and the mixture was heated for 5 minutes at of 37°C. Then 36μM oleoyl CoA containing 1-¹⁴C-oleoyl CoA was added and the whole mixture was heated for 10 minutes at 37°C. The reaction was stopped by adding chloroform/methanol (=2/1). Upon stirring, cholesterol oleate extracted into the chloroform layer was separated by thin layer chromatography and the radioactivity was then determined as ACAT activity.

Table 1

| Compound to be tested | Inhibiting activity against ACAT activity: IC (M) 50% |
|------------------------|---|
| Compound of Example 1 | 1.8x10 ⁻⁸ |
| Compound of Example 49 | 4.4x10 ⁻⁸ |

(ii) Action for lowering lipid level in blood

To a male rat (5 weeks old, Sprague-Dawley), bait containing 1.5% of cholesterol and 0.5% of bile acid was provided for 7 days, and for the last 5 days compound (I) suspended in 0.5% aqueous methylcellulose was orally administered via Sonde once per day. Two hours after the last administration, blood was gathered under etherization, and the total amount of blood cholesterol was determined according to Siedel's method [Siedel, J., et al., J. Clin. Chem. Clin. Biochem. 19, 838 (1981)] and the amount of HDL-cholesterol in blood was determined according to Ishikawa's method [Ishikawa, T.T., et al., Lipids 11, 628 (1976)]. According to these methods, compounds of formula (I) and salts thereof, administered at a dosage of 3-30 mg/Kg effectively reduced the blood cholesterol level of the male rats.

Medicaments containing (e.g. as a major component) compounds of formula (I) or salts thereof may be prepared using normal pharmaceutical carriers and excipients in conventional ways. The types of administration may include oral administration of tablets, pills, capsules, granules, powders, solutions and the

like, or parenteral administration by intravenous injection and intramuscular injection, suppositories and the like.

The dosage may be suitably determined depending upon the condition and age and sex of the subject and in the case of conventional oral administration the dosage is e.g. 50 to 500 mg per day for an adult in one or two to four doses. The following Examples and Reference Examples illustrate the present invention in more detail, and in them $^1\text{H-NMR}$ means hydrogen nuclear magnetic resonance spectrum, mp denotes melting point, Mass represents mass analysis value, and IR refers to infra red absorption spectrum. The Reference Examples show preparation of various intermediate compounds for preparation of formula (I) compounds and salts, including some intermediates of formula (XIII) above which are part of the invention.

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Reference Example 1

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To a mixture of 4.6 g heptylamine, 4.04 g triethylamine and 30 ml methylene dichloride, was added with stirring 4.06 g terephthaloyl chloride under ice cooling. Stirring was continued at room temperature for two hours, and the solid which separated out was collected by filtration, washed with methylene dichloride and water in that order, and dried, giving 6.5 g of N,N'-diheptylterephthalamide.

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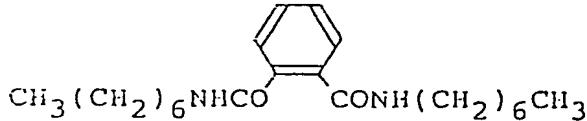
- (i) $^1\text{H-NMR}$ (CDCl_3 , δ ppm)
 - 0.88 (6H, t), 3.28 (4H, q), 7.88 (4H, s)
- (ii) Mass (EI) m/z 160 (M^+)

The following compound was prepared in much the same manner as in Reference Example 1.

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Reference Example 2

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$\text{N},\text{N}'\text{-Diheptylphthalamide}$

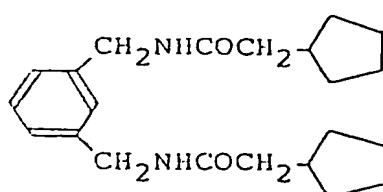
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- (i) $^1\text{H-NMR}$ (CDCl_3 , δ ppm)
 - 0.90 (6H, t), 3.38 (4H, q), 7.52 (4H, m)
- (ii) Mass (EI) m/z 360 (m^+)

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Reference Example 3

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To a mixture of 1.36 g m-xylylenediamine, 2.4 g triethylamine and 50 ml methylene dichloride, was added with stirring 3.2 g cyclopentylacetyl chloride under ice cooling. Stirring was continued at room temperature for two

hours, and the solid which separated out was collected by filtration, washed with methylene dichloride and water in that order and dried, giving 2 g of m-xylylene-cyclopentylmethyldiamine.

(i) $^1\text{H-NMR}$ (CDCl_3 , δ ppm)

4.40 (4H, d), 6.84-7.44 (4H, m)

(ii) Mass (FAB) m/z 357 ($\text{M}^+ + 1$)

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Reference Example 4 (Starting material in Example 14)



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To a mixture of 3.6 g N,N'-diheptyltetraphthalamide obtained in Example 1 and 60 ml toluene, was added dropwise 15.6 ml of a 70% solution of bis(2-methoxyethoxy)aluminum hydride in toluene. After heating under reflux for three hours, the reaction mixture was treated with 30 ml of 2.5N aqueous caustic soda solution under ice cooling, and the toluene layer separated was washed with saturated aqueous sodium chloride and dried over a drying agent. Distilling off the solvent from the dried solution gave 3.24 g of N,N'-diheptyl-p-xylylenediamine.

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(i) $^1\text{H-NMR}$ (CDCl_3 , δ ppm)

0.88 (6H, t), 3.76 (4H, s), 7.26 (4H, s)

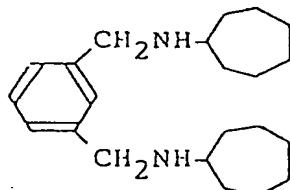
(ii) Mass (EI) m/z 332 (M^+)

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The following two compounds were prepared in much the same manner as in Reference Example 4.

Reference Example 5 (Starting material for Example 1 and other Examples. See also Reference Example 11)

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N,N'-Dicycloheptyl-m-xylylenediamine

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(i) $^1\text{H-NMR}$ (CDCl_3 , δ ppm)

3.74 (4H, s)

(ii) Mass (EI) m/z 328 (M^+)

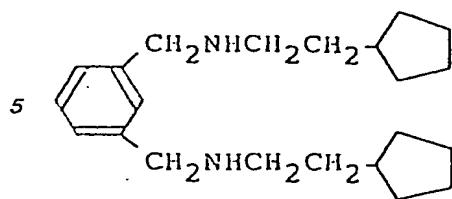
Reference Example 6 (Starting material in Example 12)

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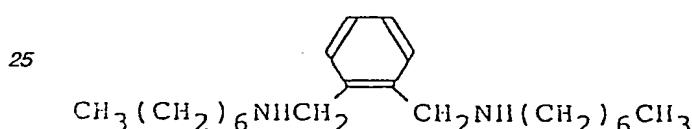
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m-Xylylene-cyclopentylethyldiamine

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 (i) $^1\text{H-NMR}$ (CDCl_3 , δ ppm)
 2.64 (4H, t), 3.80 (4H, s)
 (ii) Mass (FAB) m/z 329 ($M^+ + 1$)

20 Reference Example 7 (Starting material for Example 13)



To a 1M solution of borane-tetrahydrofuran complex (24 ml) was added dropwise under ice cooling a 5 ml tetrahydrofuran solution containing 3.6 g of N,N' -diheptylphthalimide obtained in Reference Example 2 under an argon gas stream, and the mixture was warmed up slowly and then heated under reflux for one hour. After 35 cooling, 2 ml methanol was added dropwise under ice cooling, and the mixture was heated under reflux for 30 minutes. After cooling in ice, 4.24 ml concentrated hydrochloric acid was added, and the mixture was again heated under reflux for 30 minutes. The solvent was distilled off under reduced pressure, and the residue was basified by addition of aqueous caustic soda and extracted with chloroform. After distilling off the chloroform from the extract, the residue was purified by silica gel column chromatography, giving 0.43 g of 40 N,N' -diheptyl-o-xylylenediamine.

(i) $^1\text{H-NMR}$ (CDCl_3 , δ ppm)
 0.88 (6H, t), 2.64 (4H, t), 3.80 (4H, s)
 (ii) Mass (Cl) m/z 333 ($M^+ + 1$)

45 Reference Example 8

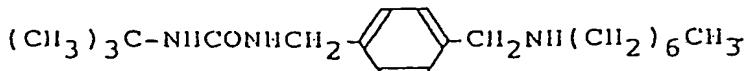


To a solution of 2.7 g p-xylylenediamine in 100 ml methylene dichloride, was added slowly with stirring 10 ml of a n-hexane solution containing 990 mg t-butyl isocyanate under ice cooling. Stirring was continued at room temperature for two hours, the solvent was distilled off under reduced pressure, and the residue was purified by silica gel column chromatography, giving 1 g of 4-(3-t-butylureidomethyl)-1-aminomethylbenzene.

(i) $^1\text{H-NMR}$ (CDCl_3 , δ ppm)
 1.32 (9H, s), 3.84 (2H, s), 7.24 (4H, s)
 (ii) Mass (EI) m/z 235 (M^+)

Reference Example 9 (Starting material in Example 3)

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A mixture of 0.97 g 4-(3-t-butylureidomethyl)-1-aminomethylbenzene obtained in Reference Example 8, 0.57 g anhydrous potassium carbonate and 20 ml dimethylformamide was stirred at room temperature for 30 minutes, 0.93 g 1-iodoheptane was added, and stirring was continued at room temperature for an additional three hours. After distilling off the solvent under reduced pressure, the residue was extracted with chloroform, and the extract was washed with water. The chloroform was distilled off under reduced pressure, and the residue was purified by silica gel column chromatography, giving 0.65 g of 4-(3-t-butylureido-methyl)-1-(N-heptylaminomethyl)benzene.

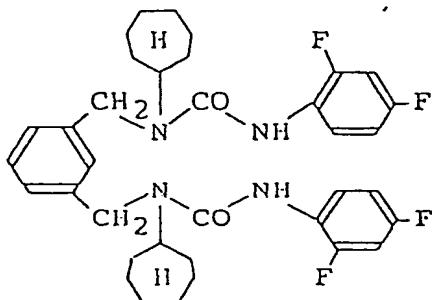
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- (i) $^1\text{H-NMR}$ (CDCl_3 , δ ppm)
0.88 (3H, t), 2.60 (2H, t), 3.72 (2H, s)
- (ii) Mass (EI) m/z 333 (M^+)

15

Example 1

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To a solution of 1 g *N,N'*-dicycloheptyl-*m*-xylylenediamine in 50 ml *n*-hexane, was added dropwise with stirring 5 ml of a *n*-hexane solution containing 1 g 2,4-difluorophenyl isocyanate under ice cooling. Stirring was continued at room temperature for two hours, the solvent was distilled off under reduced pressure, and the residue was purified by silica gel column chromatography and then recrystallized from isopropanol, giving 1.6 g of 1,3-bis[[1-cycloheptyl-3-(2,4-difluorophenyl)ureido]methyl]benzene.

40

- (i) M.p. 71-72°C
- (ii) Mass (FAB) m/z 639 ($M^+ + 1$)
- (iii) Elemental analysis ($C_{36}H_{42}N_4O_2F_4$)

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| | C | H | N |
|------------|-------|------|------|
| Calcd. (%) | 67.69 | 6.63 | 8.77 |
| Found (%) | 67.68 | 6.71 | 8.74 |

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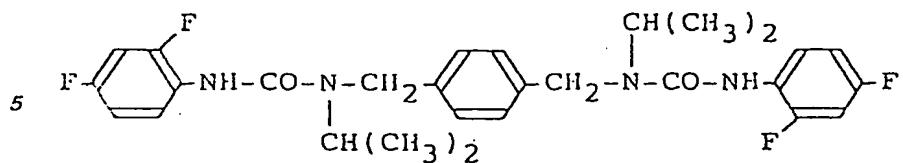
The following four compounds were prepared in much the same manner as in Example 1.

Example 2

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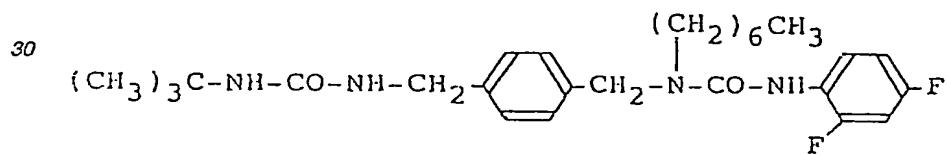
10 1,4-Bis[[3-(2,4-difluorophenyl)-1-isopropylureido]-methyl]benzene

15 (i) M.p. 167-168°C
 (ii) Mass (FAB) m/z 531 (M⁺ + 1)
 (iii) Elemental analysis (C₂₈H₃₀N₄O₂F₄)

20

| | C | H | N |
|------------|-------|------|-------|
| Calcd. (%) | 66.39 | 5.70 | 10.56 |
| Found (%) | 63.40 | 5.93 | 10.42 |

25 Example 3



35 1-[p-(3-t-Butylureidomethyl)benzyl]-3-(2,4-difluoro-phenyl)-1-heptylurea

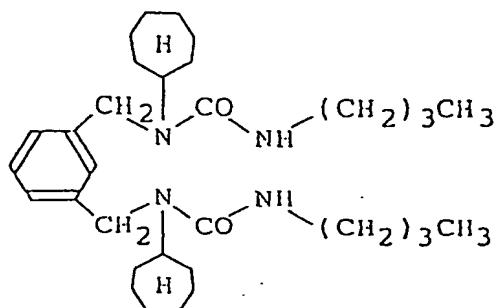
45 (i) M.p. 117-119°C
 (ii) Mass (EI) m/z 489 (M⁺ + 1)
 (iii) Elemental analysis (C₂₇H₃₈N₄O₂F₂)

| | C | H | N |
|------------|-------|------|-------|
| Calcd. (%) | 66.37 | 7.84 | 11.47 |
| Found (%) | 66.40 | 7.81 | 11.45 |

55 Example 4

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1,3-Bis[(3-butyl-1-cycloheptylyureido)methyl]benzene

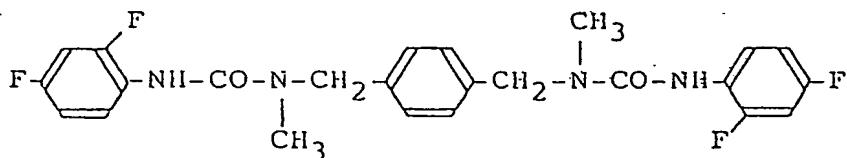
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- (i) M.p. 132-133°C
(ii) Mass (FAB) m/z 527 ($M^+ + 1$)
(iii) Elemental analysis (C₃₂H₅₄N₄O₂)

| | C | H | N |
|------------|-------|-------|-------|
| Calcd. (%) | 72.96 | 10.33 | 10.64 |
| Found (%) | 72.72 | 10.24 | 10.44 |

Example 5

35

**1,4-Bis[3-(2,4-difluorophenyl)-1-methylureido]-methylbenzene**

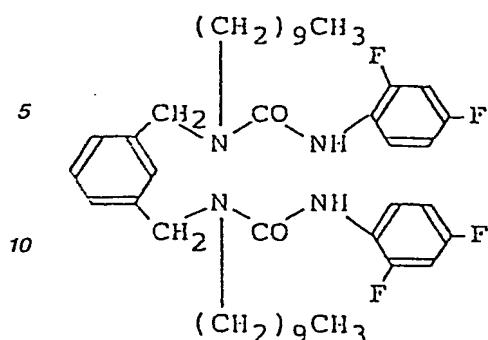
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- (i) M.p. 196-198°C
(ii) Mass (FAB) m/z 475 ($M^+ + 1$)
(iii) Elemental analysis (C₂₄H₂₂N₄O₂F₄)

| | C | H | N |
|------------|-------|------|-------|
| Calcd. (%) | 60.76 | 4.67 | 11.81 |
| Found (%) | 60.81 | 4.82 | 11.61 |

Example 6

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15

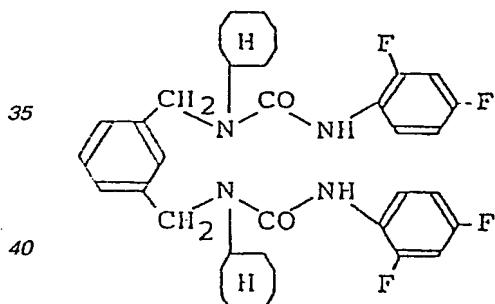
To a solution of 833 mg N,N'-didecyl-m-xylylenediamine in 20 ml n-hexane, was added dropwise with stirring 5 ml of a n-hexane solution containing 620 mg 2,4-difluorophenyl isocyanate under ice cooling. Stirring was continued at room temperature for two hours, the solvent was distilled off under reduced pressure, and the residue was purified by silica gel column chromatography, giving 750 mg of 1,3-bis[[1-decyl-3-(2,4-difluorophenyl)ureido]methyl]benzene.

(i) $^1\text{H-NMR}$ (CDCl_3 , δ ppm)
 0.88 (6H, t), 3.36 (4H, t), 4.60 (4H, s)

The following seven compounds were prepared in much the same manner as in Example 6.

Example 7

30



45

1,3-Bis[[1-cyclooctyl-3-(2,4-difluorophenyl)ureido]-methyl]benzene

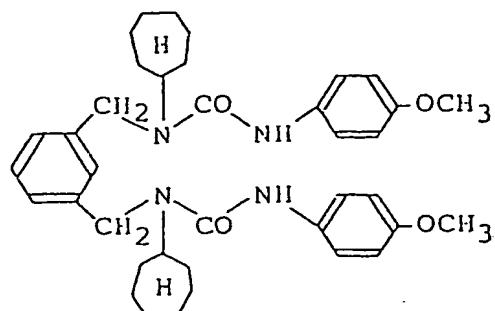
50

(i) $^1\text{H-NMR}$ (CDCl_3 , δ ppm)
 4.48 (4H, s), 6.24 (1H, d), 8.02 (1H, m)
 (ii) Mass (FAB) m/z 667 ($\text{M}^+ + 1$)
 (iii) IR (cm^{-1}), 1672, 1536, 1432, 1198

Example 8

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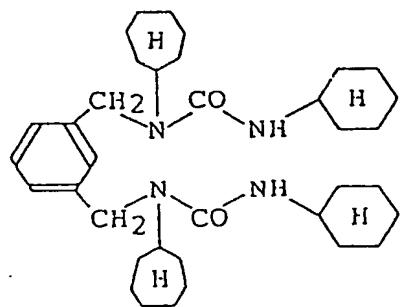
1,3-Bis[(1-cycloheptyl-3-(p-methoxyphenyl)ureido)-
methyl]benzene

20

(i) $^1\text{H-NMR}$ (CDCl_3 , δ ppm)
3.74 (6H, s), 4.52 (4H, s), 6.68 (4H, d)
(ii) Mass (FAB) m/z 627 ($M^+ + 1$)
(iii) IR (cm^{-1}), 1646, 1514, 1232

25

Example 9



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1,3-Bis[(1-cycloheptyl-3-cyclohexylureido)methyl]benzene

45

(i) $^1\text{H-NMR}$ (CDCl_3 , δ ppm)
4.32 (4H, s)
(ii) Mass (FAB) m/z 579 ($M^+ + 1$)
(iii) IR (cm^{-1}), 2860, 1636, 1530

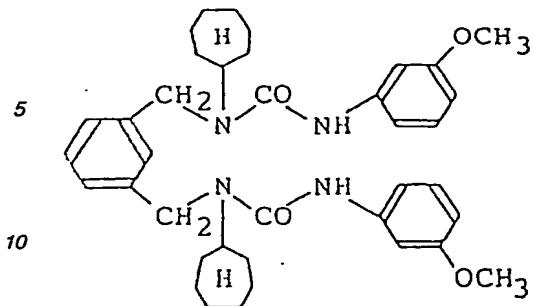
50

Example 10

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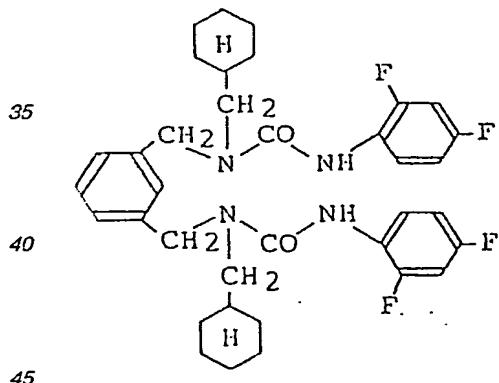
15

1,3-Bis[[1-cycloheptyl-3-(m-methoxyphenyl)ureido]-
20 methyl]benzene

25 (i) $^1\text{H-NMR}$ (CDCl_3 , δ ppm)
3.76 (6H, s), 4.48 (4H, s)
(ii) Mass (FAB) m/z 627 ($M^+ + 1$)
(iii) IR (cm^{-1}), 1654, 1608, 1540, 1496, 1456

Example 11

30



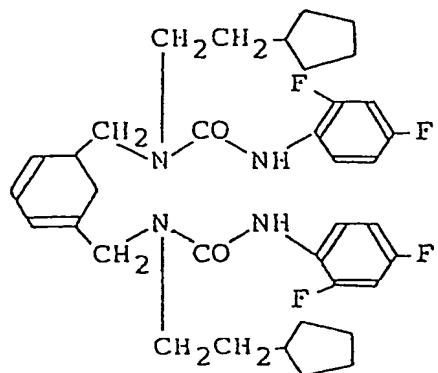
1,3-Bis[[3-(2,4-difluorophenyl)-1-cyclohexylmethyl-
50 ureido]methyl]benzene

55 (i) $^1\text{H-NMR}$ (CDCl_3 , δ ppm)
3.18 (4H, d), 3.58 (4H, s), 6.42 (1H, d)
(ii) Mass (FAB) m/z 639 ($M^+ + 1$)
(iii) IR (cm^{-1}), 2936, 1654, 1616, 1524

Example 12

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20
1,3-Bis[(3-(2,4-difluorophenyl)-1-cyclopentylethyl-
ureido)methyl]benzene

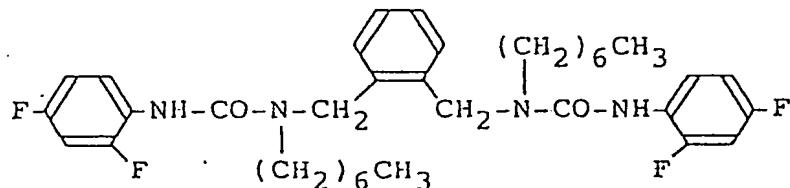
25

30

- (i) $^1\text{H-NMR}$ (CDCl_3 , δ ppm)
3.36 (4H, t), 4.60 (4H, s), 6.42 (1H, d)
- (ii) Mass (FAB) m/z 439 ($M^+ - 1$)
- (iii) IR (cm^{-1}), 2960, 1652, 1616, 1532, 1434

35

Example 13



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50
1,2-Bis[(3-(2,4-difluorophenyl)-1-heptylureido)-
methyl]benzene

50

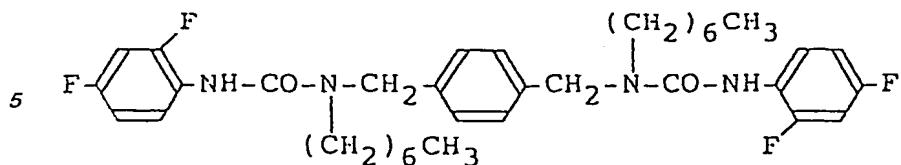
- (i) $^1\text{H-NMR}$ (CDCl_3 , δ ppm)
0.88 (6H, t), 3.36 (4H, t), 4.68 (4H, s)
- (ii) Mass (FAB) m/z 643 ($M^+ + 1$)

55

Example 14

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To a solution of 1.5 g N,N'-diheptyl-p-xylylenediamine in 20 ml n-hexane, was added dropwise with stirring 5 ml of a n-hexane solution containing 1.4 g 2,4-difluorophenyl isocyanate under ice cooling. Stirring was continued at room temperature for two hours, and the solid which separated out was collected by filtration and recrystallized from methanol, giving 2.3 g of 1,4-bis[1-heptyl-3-(2,4-difluorophenyl)ureido]methyl]benzene.

15

- (i) M.p. 107-108°C
- (ii) Mass (EI) m/z 642 (M⁺)
- (iii) Elemental analysis (C₃₆H₄₆N₄O₂F₄)

20

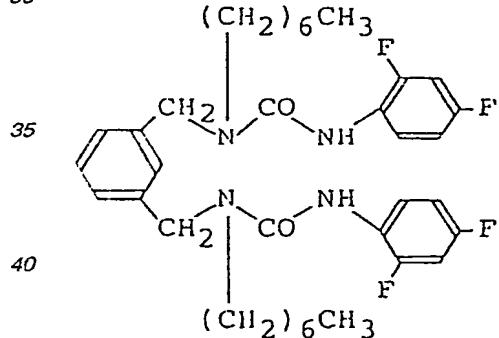
| | C | H | N |
|------------|-------|------|------|
| Calcd. (%) | 67.27 | 7.21 | 8.72 |
| Found (%) | 67.23 | 7.25 | 8.71 |

25

The following twelve compounds were prepared in much the same manner as in Example 14.

Example 15

30



45

1,3-Bis[[3-(2,4-difluorophenyl)-1-heptylureido]-methyl]benzene

50

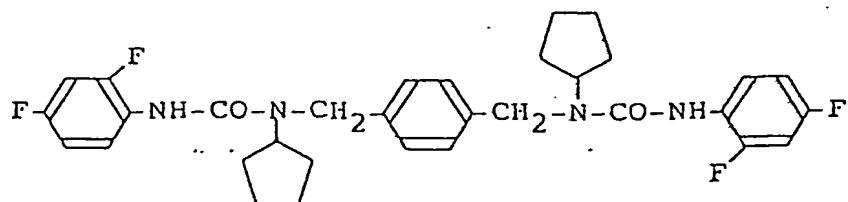
- (i) M.p. 69-70°C
- (ii) Mass (FAB) m/z 643 (M⁺ + 1)
- (iii) Elemental analysis (C₃₆H₄₆N₄O₂F₄)

55

| | C | H | N |
|------------|-------|------|------|
| Calcd. (%) | 67.27 | 7.21 | 8.72 |
| Found (%) | 67.23 | 7.33 | 8.70 |

Example 16

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10

1,4-Bis[[1-cyclopentyl-3-(2,4-difluorophenyl)ureido]-methyl]benzene.

15

(i) M.p. 165-167°C

(ii) Mass (FAB) m/z 583 (M⁺ + 1)(iii) Elemental analysis (C₃₂H₃₄N₄O₂F₄)

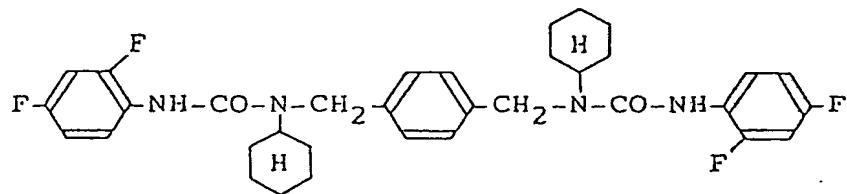
20

| | C | H | N |
|------------|-------|------|------|
| Calcd. (%) | 65.97 | 5.88 | 9.62 |
| Found (%) | 65.96 | 5.94 | 9.58 |

25

Example 17

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35

1,4-Bis[[1-cyclohexyl-3-(2,4-difluorophenyl)ureido]-methyl]benzene.

40

(i) M.p. 176-177°C

(ii) Mass (FAB) m/z 611 (M⁺ + 1)(iii) Elemental analysis (C₃₄H₃₈N₄O₂F₄)

45

| | C | H | N |
|------------|-------|------|------|
| Calcd. (%) | 66.87 | 6.27 | 9.17 |
| Found (%) | 66.69 | 6.28 | 9.08 |

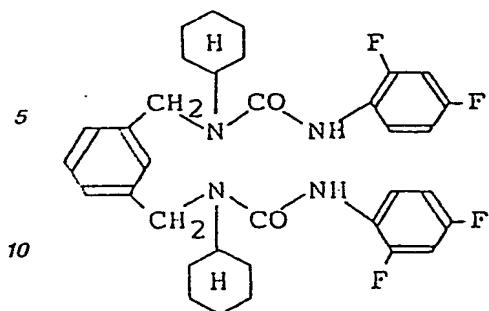
50

Example 18

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15 1,3-Bis[(1-cyclohexyl-3-(2,4-difluorophenyl)ureido)-
methyl]benzene.

20

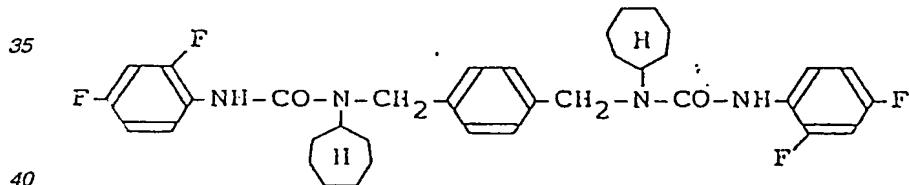
(i) M.p. 98-99°C
(ii) Mass (FAB) m/z 611 ($M^+ + 1$)
(iii) Elemental analysis (C₃₄H₃₈N₄O₂F₄)

25

| | C | H | N |
|------------|-------|------|------|
| Calcd. (%) | 66.87 | 6.27 | 9.17 |
| Found (%) | 66.99 | 6.21 | 8.96 |

30

Example 19



45 1,4-Bis[(1-cycloheptyl-3-(2,4-difluorophenyl)ureido)-
methyl]benzene.

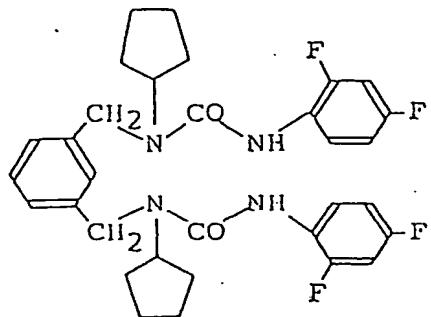
50

55 (i) M.p. 89-91°C
(ii) Mass (FAB) m/z 639 ($M^+ + 1$)
(iii) Elemental analysis (C₃₆H₄₂N₄O₂F₄)

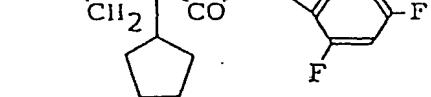
| | C | H | N |
|------------|-------|------|------|
| Calcd. (%) | 67.69 | 6.63 | 8.77 |
| Found (%) | 67.62 | 6.81 | 8.62 |

Example 20

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1,3-Bis[(1-cyclopentyl-3-(2,4-difluorophenyl)ureido)methyl]benzene.

20

(i) M.p. 150-151°C

(ii) Mass (TAB) m/z 583 (M⁺ + 1)(iii) Elemental analysis (C₃₂H₃₄N₄O₂F₄)

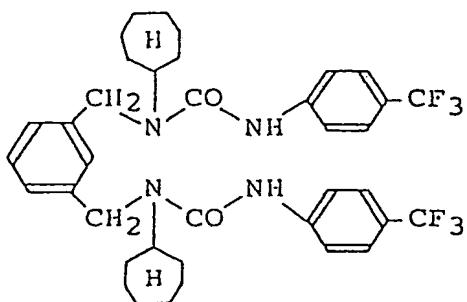
25

| | C | H | N |
|------------|-------|------|------|
| Calcd. (%) | 65.97 | 5.88 | 9.62 |
| Found (%) | 65.73 | 5.97 | 9.60 |

30

Example 21

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40

1,3-Bis[(1-cyclopentyl-3-(p-trifluoromethylphenyl)ureido)methyl]benzene

55

(i) M.p. 169-170°C

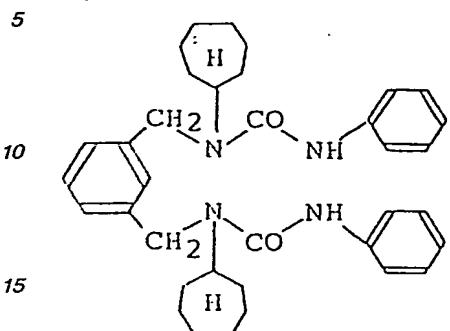
(ii) Mass (FAB) m/z 703 (M⁺ + 1)(iii) Elemental analysis (C₃₈H₄₄N₄O₂F₆)

60

| | C | H | N |
|------------|-------|------|------|
| Calcd. (%) | 64.94 | 6.31 | 7.97 |
| Found (%) | 64.89 | 6.35 | 7.94 |

65

Example 22



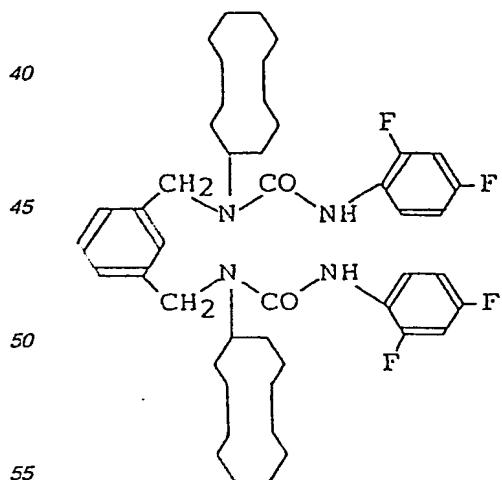
20
1,3-Bis[(1-cyclohexyl-3-phenylureido)methyl]benzene

25
(i) M.p. 160-162°C
(ii) Mass (FAB) m/z 567 ($M^+ + 1$)
(iii) Elemental analysis (C₃₆H₄₆N₄O₂)

30

| | C | H | N |
|------------|-------|------|------|
| Calcd. (%) | 76.29 | 8.18 | 9.88 |
| Found (%) | 76.27 | 8.32 | 9.83 |

35
Example 23



60
1,3-Bis[[1-cyclododecyl-3-(2,4-difluorophenyl)ureido]-methyl]benzene

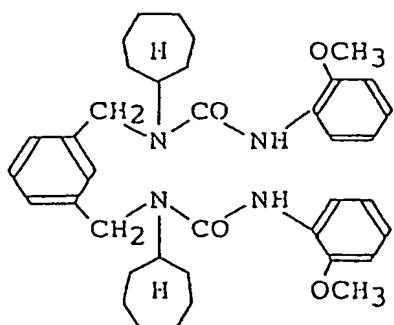
- (i) M.p. 166-167°C
(ii) Mass (FAB) m/z 779 ($M^+ + 1$)
(iii) Elemental analysis (C₄₆H₆₂N₄O₂F₄)

5

| | C | H | N |
|------------|-------|------|------|
| Calcd. (%) | 70.92 | 8.02 | 7.19 |
| Found (%) | 71.01 | 8.16 | 7.05 |

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Example 24



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1,3-Bis[[1-cycloheptyl-3-(o-methoxyphenyl)ureido]-methyl]benzene

30

- (i) M.p. 160-162°C
(ii) Mass (FAB) m/z 627 ($M^+ + 1$)
(iii) Elemental analysis (C₃₈H₅₀N₄O₄)

35

| | C | H | N |
|------------|-------|------|------|
| Calcd. (%) | 72.81 | 8.04 | 8.94 |
| Found (%) | 72.78 | 8.07 | 8.90 |

40

Example 25

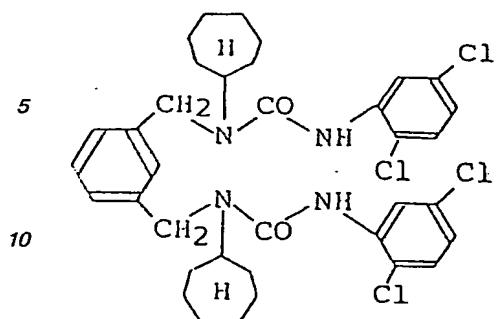
45

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15 1,3-Bis[[1-cycloheptyl-3-(2,5-dichlorophenyl)ureido]methyl]benzene

20

- (i) M.p. 153-155°C
- (ii) Mass (FAB) m/z 705 ($M^+ + 1$)
- (iii) Elemental analysis (C₃₆H₄₂N₄O₂Cl₄)

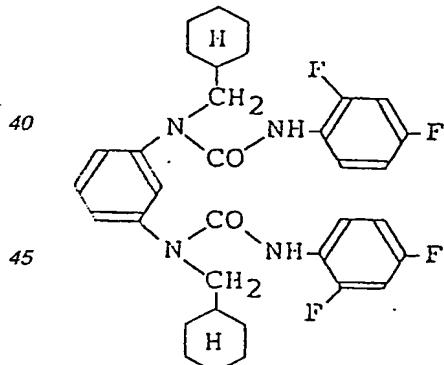
25

| | C | H | N |
|------------|-------|------|------|
| Calcd. (%) | 61.37 | 6.01 | 7.95 |
| Found (%) | 61.27 | 5.93 | 7.93 |

30

Example 26

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55 1,3-Bis[1-cyclohexylmethyl-3-(2,4-difluorophenyl)ureido]benzene

60

- (i) M.p. 183-185°C
- (ii) Mass (FAB) m/z 611 ($M^+ + 1$)
- (iii) Elemental analysis (C₃₄H₃₈N₄O₂F₄)

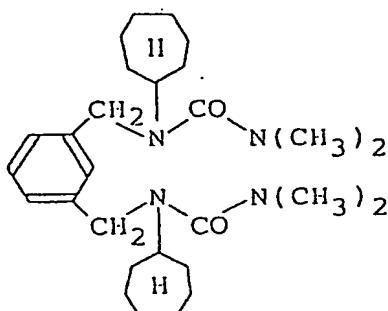
65

| | C | H | N |
|------------|-------|------|------|
| Calcd. (%) | 66.87 | 6.27 | 9.17 |
| Found (%) | 66.72 | 6.40 | 9.09 |

5

Example 27

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To a solution of 0.6 g N,N'-dicycloheptyl-m-xylylenediamine and 0.44 g triethylamine in 20 ml methylene dichloride, was added dropwise 5 ml of a methylene dichloride solution containing 0.47 g N,N-dimethylcarbamic chloride, and stirring was continued at room temperature for 12 hours. The reaction mixture was washed with water, dilute hydrochloric acid and water in that order, and dried over a drying agent. After distilling off the solvent, the residue was purified by silica gel column chromatography, giving 0.24 g of 1,3-bis[(1-cycloheptyl-3,3-dimethylureido)methyl]benzene as oil.

30

(i) $^1\text{H-NMR}$ (CDCl_3 , δ ppm)

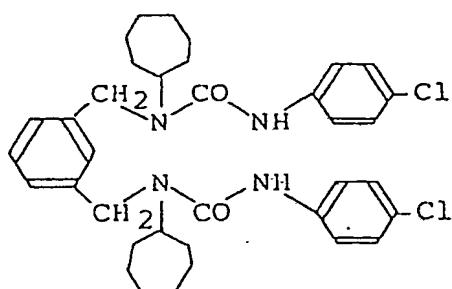
2.80 (12H, s), 4.24 (4H, s)

35

(ii) Mass (FAB) m/z 471 ($M^+ + 1$)(iii) IR (cm^{-1}), 1654, 1492, 1460, 1174

Example 28

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To a solution of 0.5 g N,N'-dicycloheptyl-m-xylylenediamine in 50 ml n-hexane, was added dropwise with stirring 5 ml of a n-hexane solution containing 0.25 g 4-chlorophenyl isocyanate under ice cooling, and stirring was continued at room temperature for two hours. After distilling off the solvent under reduced pressure, the residue was purified by silica gel column chromatography, giving 0.9 g of 1,3-bis[[3-(p-chlorophenyl)-1-cycloheptylureido]methyl]benzene as amorphous solid.

60

(i) $^1\text{H-NMR}$ (CDCl_3 , δ ppm)

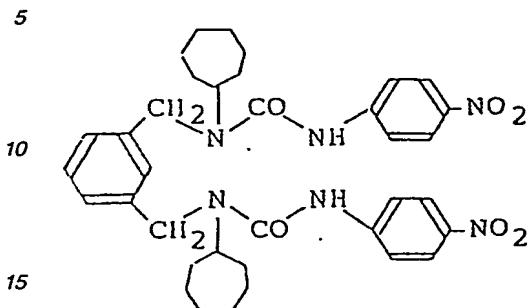
1.20-2.20 (26H, m), 4.48 (4H, s), 1.12 (2H, s)

(ii) Mass (FAB) m/z 635 (M^+)(iii) IR (cm^{-1}) 1646, 1526, 1496

The following two compounds were prepared in much the same manner as in Example 28.

65

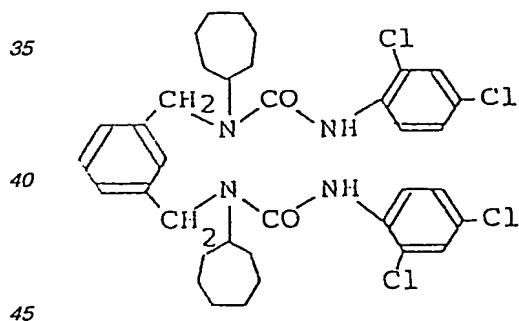
Example 29



20 1,3-Bis[[1-cycloheptyl-3-(p-nitrophenyl)ureido]-methyl]benzene

25 (i) $^1\text{H-NMR}$ (CDCl_3 , δ ppm)
4.52 (4H, s), 6.56 (2H, s), 8.04 (4H, d)
(ii) Mass (FAB) m/z 657 ($M^+ + 1$)
(iii) IR (cm^{-1}), 1674, 1542, 1504, 1334

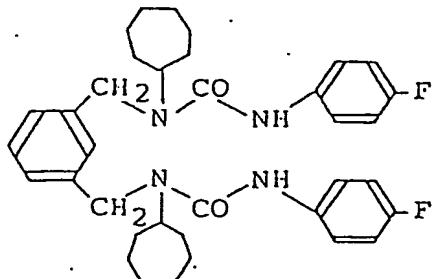
30 Example 30



50 1,3-Bis[[1-cycloheptyl-3-(2,4-dichlorophenyl)ureido]-methyl]benzene

55 (i) $^1\text{H-NMR}$ (CDCl_3 , δ ppm)
4.56 (4H, s), 6.75 (2H, s), 8.18 (2H, d)
(ii) Mass (FAB) m/z 765 ($M^+ + 1$)
(iii) IR (cm^{-1}), 1678, 1582, 1518, 1302

60 Example 31



To a solution of 0.5 g N,N'-dicycloheptyl-m-xylylenediamine in 50 ml n-hexane, was added dropwise with stirring 5 ml of a n-hexane solution containing 0.46 g 4-fluorophenyl isocyanate under ice cooling, and stirring was continued at room temperature for two hours. The solid which separated out was collected by filtration, washed with n-hexane and recrystallized from methanol, giving 0.75 g of 1,3-bis[[1-cycloheptyl-3-(p-fluorophenyl)ureido]methyl]benzene.

(i) M.p. 183-185°C

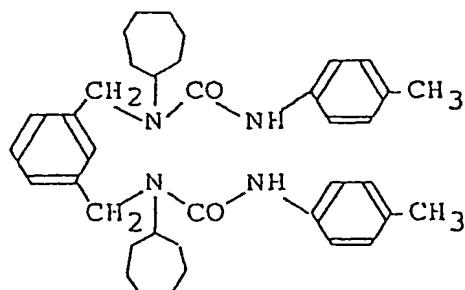
(ii) Mass (FAB) m/z 603 (M⁺ + 1)

(iii) Elemental analysis (C₃₆H₄₄N₄O₂F₂)

| | C | H | N |
|------------|-------|------|------|
| Calcd. (%) | 71.74 | 7.36 | 9.29 |
| Found (%) | 71.70 | 7.37 | 9.29 |

The following seven compounds were prepared in much the same manner as in Example 31.

Example 32



1,3-Bis[[1-cycloheptyl-3-(p-tolyl)ureido]-methyl]benzene

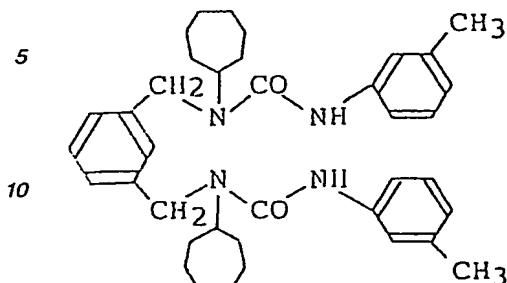
(i) M.p. 147-148°C

(ii) Mass m/z 595 (M⁺ + 1)

(iii) Elemental analysis (C₃₈H₅₀N₄O₂)

| | C | H | N |
|------------|-------|------|------|
| Calcd. (%) | 76.73 | 8.47 | 9.42 |
| Found (%) | 76.65 | 8.54 | 9.27 |

Example 33



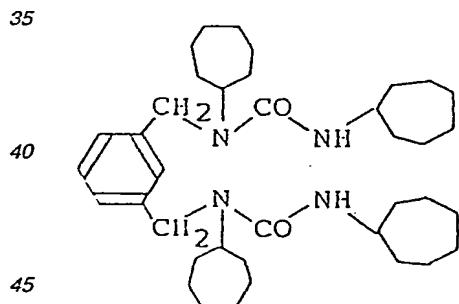
1,3-Bis[(1-cycloheptyl-3-(m-tolyl)ureido)-
methyl]benzene

20

- (i) M.p. 171-173°C
 (ii) Mass m/z 595 ($M^+ + 1$)
 25 (iii) Elemental analysis (C₃₈H₅₀N₄O₂)

| | C | H | N |
|--------------|-------|------|------|
| Calcd. (%) | 76.73 | 8.47 | 9.42 |
| 30 Found (%) | 76.65 | 8.54 | 9.27 |

Example 34

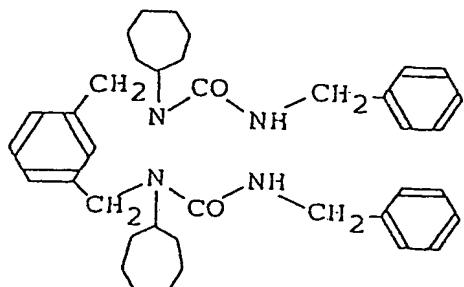


50 1,3-Bis[(1,3-dicycloheptylureido)methyl]benzene

- 55 (i) M.p. 165-167°C
 (ii) Mass m/z 607 ($M^+ + 1$)
 (iii) Elemental analysis (C₃₈H₆₂N₄O₂)

| | C | H | N |
|---------------|-------|-------|------|
| 60 Calcd. (%) | 75.20 | 10.30 | 9.23 |
| Found (%) | 74.90 | 10.44 | 8.95 |

65 Example 35



20

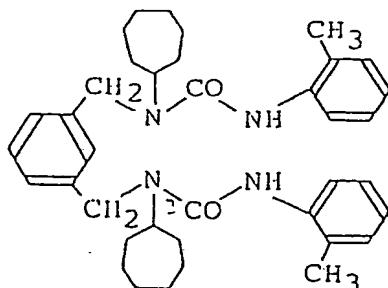
1,3-Bis[(3-benzyl-1-cycloheptylureido)-methyl]benzene

- 25
- (i) M.p. 173-174°C
 - (ii) Mass (FAB) m/z 595 ($M^+ + 1$)
 - (iii) Elemental analysis (C₃₈H₅₀N₄O₂)

| | C | H | N | 30 |
|------------|-------|------|------|----|
| Calcd. (%) | 76.73 | 8.47 | 9.42 | |
| Found (%) | 76.74 | 8.52 | 9.35 | |

35

Example 36



55

1,3-Bis[[1-cycloheptyl-3-(o-tolyl)ureido]-methyl]benzene

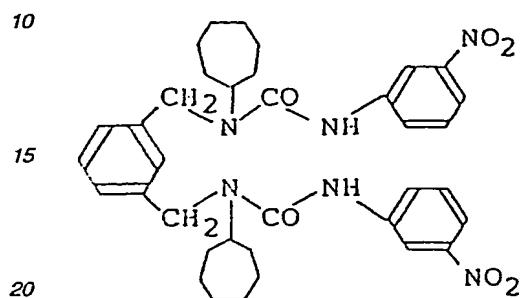
- 60
- (i) M.p. 183-185°C
 - (ii) Mass (FAB) m/z 595 ($M^+ + 1$)
 - (iii) Elemental analysis

65

| | C | H | N |
|------------|-------|------|------|
| Calcd. (%) | 76.73 | 8.47 | 9.42 |
| Found (%) | 76.67 | 8.50 | 9.33 |

5

Example 37

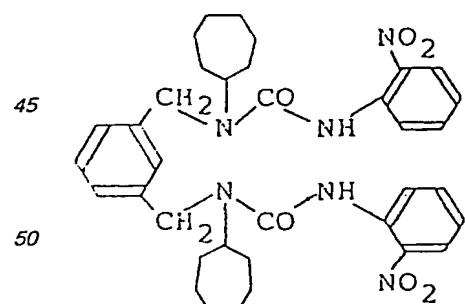


25 1,3-Bis[[1-cycloheptyl-3-(m-nitrophenyl)ureido]-
methyl]benzene

- 30 (i) M.p. 200-201°C
(ii) Mass (FAB) m/z 657 ($M^+ + 1$)
(iii) Elemental analysis (C₃₆H₄₄N₆O₆)

| | C | H | N |
|--------------------|-------|------|-------|
| 35 Calcd. (%) | 65.84 | 6.75 | 12.80 |
| Found (%) | 65.53 | 6.68 | 12.84 |

40 Example 38



55 1,3-Bis[[1-cycloheptyl-3-(o-nitrophenyl)ureido]-
methyl]benzene

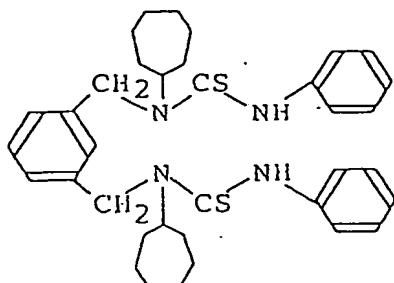
- 60 (i) M.p. 144-145°C
(ii) Mass (FAB) m/z 657 ($M^+ + 1$)
(iii) Elemental analysis (C₃₆H₄₄N₆O₆)

| | C | H | N |
|------------|-------|------|-------|
| Calcd. (%) | 65.84 | 6.75 | 12.80 |
| Found (%) | 65.63 | 6.71 | 12.86 |

5

Example 39

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To a solution of 0.5 g N,N'-dicycloheptyl-m-xylylenediamine in 50 ml n-hexane, was added dropwise with stirring 5 ml of a n-hexane solution containing 0.45 g phenyl isothiocyanate under ice cooling, and stirring was continued at room temperature for two hours. The solid which separated out was collected by filtration, and recrystallized from methanol, giving 0.65 g of 1,3-bis[[1-cycloheptyl-3-phenyl(thioureido)methyl]benzene.

25

(i) M.p. 146-148°C

30

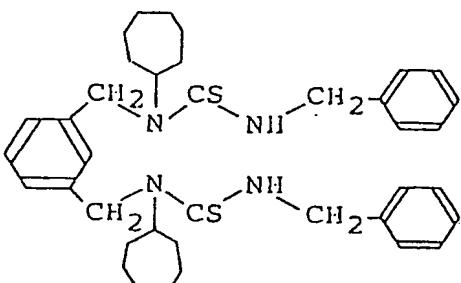
(ii) Mass (FAB) m/z 599 (M⁺ + 1)(iii) Elemental analysis (C₃₆H₄₆N₄S₂)

| | C | H | N |
|------------|-------|------|------|
| Calcd. (%) | 72.20 | 7.74 | 9.35 |
| Found (%) | 72.21 | 7.84 | 9.07 |

35

Example 40

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To a solution of 0.5 g N,N'-dicycloheptyl-m-xylylenediamine in 50 ml n-hexane, was added dropwise with stirring 5 ml of a n-hexane solution containing 0.5 g benzyl isothiocyanate under ice cooling, and stirring was continued at room temperature for 12 hours. After distilling off the solvent under reduced pressure, the residue was purified by silica gel column chromatography, giving 0.78 g of 1,3-bis[3-benzyl-1-cycloheptyl(thioureido)methyl]benzene as amorphous solid.

60

(i) ¹H-NMR (CDCl₃, δ ppm)

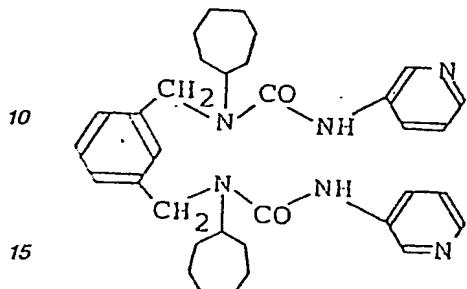
4.56 (4H, s), 4.74 (4H, d)

(ii) Mass (FAB) m/z 627 (M⁺ + 1)(iii) IR (cm⁻¹), 1526, 1380, 1324

65

Example 41

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20 To a solution of 0.5 g N,N'-dicycloheptyl-m-xylylenediamine in 30 ml anhydrous toluene, was added 0.5 g β -pyridinecarboxylic azide, and the mixture was heated under reflux for one hour. After confirming cessation of gas evolution, the solvent was distilled off under reduced pressure, and the residue was purified by silica gel column chromatography and then recrystallized from diethyl ether, giving 0.5 g of 1,3-bis[[1-cycloheptyl-3-(3-pyridyl)ureido]methyl]benzene.

25 (i) M.p. 125-127°C

(ii) Mass (FAB) m/z 569 ($M^+ + 1$)

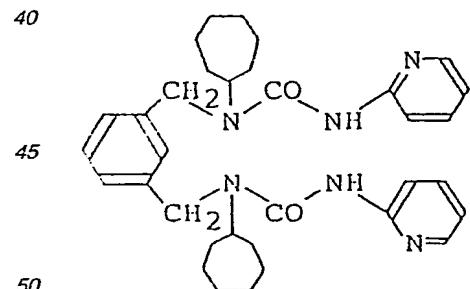
(iii) Elemental analysis (C₃₄H₄₄N₆O₂)

| | C | H | N |
|------------|-------|------|-------|
| Calcd. (%) | 71.80 | 7.80 | 14.78 |
| Found (%) | 71.97 | 7.76 | 14.65 |

The following three compounds were prepared in much the same manner as in Example 41.

35

Example 42



55

1,3-Bis[[1-cycloheptyl-3-(2-pyridyl)ureido]-methyl]benzene

60

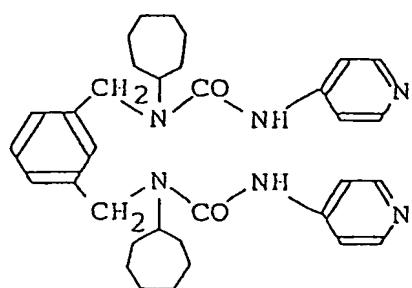
(i) ¹H-NMR (CDCl₃, δ ppm)

4.55 (4H, s), 7.56 (2H, dd), 7.65 (2H, dd)

(ii) Mass (FAB) m/z 569 ($M^+ + 1$)

(iii) IR (cm⁻¹), 1670, 1518, 1434, 1302

Example 43

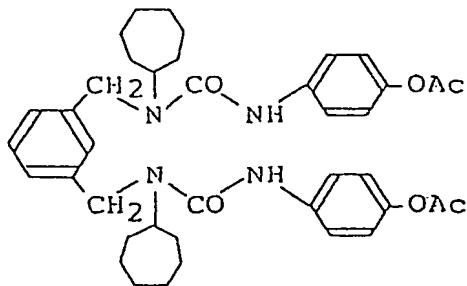


1,3-Bis[[1-cycloheptyl-3-(4-pyridyl)ureido]-
methyl]benzene.

- (i) M.p. 119-121°C
- (ii) Mass (FAB) m/z 569 ($M^+ + 1$)
- (iii) Elemental analysis (C₃₄H₄₄N₆O₂)

| | C | H | N |
|------------|-------|------|-------|
| Calcd. (%) | 71.80 | 7.80 | 14.78 |
| Found (%) | 71.68 | 7.77 | 14.87 |

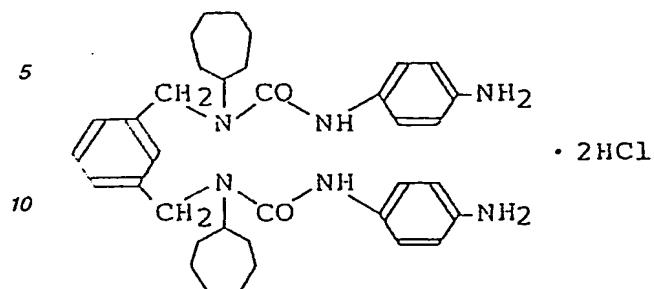
Example 44



1,3-Bis[[3-(p-acetoxyphenyl)-1-cycloheptylureido]-
methyl]benzene

- 1,3-Bis[[3-(p-acetoxyphenyl)-1-cycloheptylureido]methyl]benzene
- (i) ¹H-NMR (CDCl₃, δ ppm)
2.28 (6H, s), 4.50 (4H, s), 6.90 (4H, dd)
 - (ii) Mass (FAB) m/z 683 ($M^+ + 1$)
 - (iii) IR (cm⁻¹), 1766, 1652, 1532, 1510

Example 45



To a solution of 3 g 1,3-bis[[1-cycloheptyl-3-(p-nitrophenyl)ureido]methyl]benzene (compound of Example 30) in 50 ml N,N'-dimethylformamide, was added 300 ml of 10% Pd-carbon powder, and the mixture was subjected to catalytic hydrogenation. After a predetermined volume of hydrogen gas was absorbed, the catalyst was filtered off, the solvent was distilled off under reduced pressure from the filtrate, and the residue was purified by silica gel column chromatography, giving 1.5 g of 1,3-bis[[3-(p-aminophenyl)-1-cycloheptylureido]methyl]benzene as amorphous powder. This was treated with ethanolic hydrogen chloride, and the solid thus obtained was recrystallized from aqueous ethanol, affording 1.1 g of 1,3-bis[[1-cycloheptyl-3-(p-aminophenyl)ureido]methyl]benzene dihydrochloride.

(i) M.p. 228-232°C (dec.)

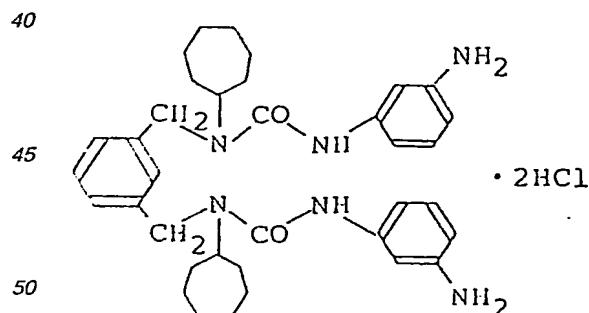
(ii) Mass (FAB) m/z 597 ($M^+ + 1$)

(iii) Elemental analysis ($C_{36}H_{50}N_6O_2Cl_2$)

| | C | H | N |
|------------|-------|------|-------|
| Calcd. (%) | 64.56 | 7.52 | 12.55 |
| Found (%) | 64.28 | 7.53 | 12.48 |

The following two compounds were prepared in much the same manner as in Example 45.

Example 46



1,3-Bis[[3-(m-aminophenyl)-1-cycloheptylureido]-methyl]benzene dihydrochloride

(i) $^1\text{H-NMR}$ (DMSO-d₆, δ ppm)

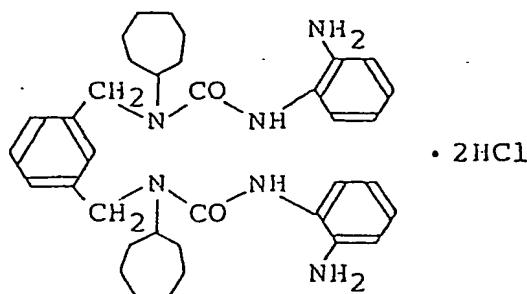
4.56 (4H, s), 8.60 (2H, s)

(ii) Mass (FAB) m/z 597 ($M^+ + 1$)

(iii) IR (cm⁻¹), 1642, 1610, 1542, 1496

Example 47

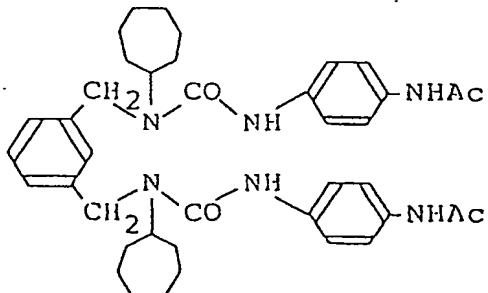
5



1,3-Bis[[3-(o-aminophenyl)-1-cycloheptylureido]-
methyl]benzene dihydrochloride

- (i) ¹H-NMR (DMSO-d₆, δ ppm)
4.56 (4H, s), 8.65 (2H, s)
- (ii) Mass (FAB) m/z 597 (M⁺ + 1)
- (iii) IR (cm⁻¹), 1636, 1522, 1458

Example 48

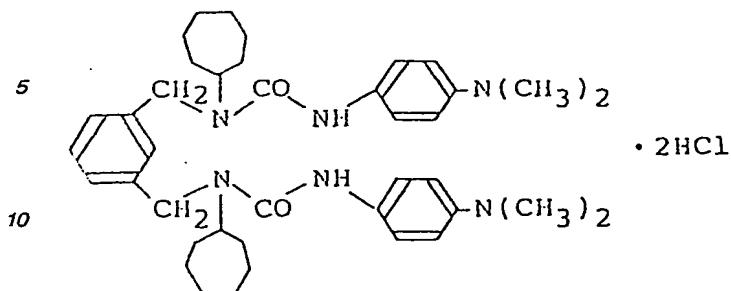


To a solution of 0.29 g 1,3-bis[[3-(p-aminophenyl)-1-cycloheptylureido]methyl]benzene (compound of Example 45) and 0.12 g triethylamine in 30 ml dichloromethane, was added dropwise with stirring 5 ml of a dichloromethane solution containing 92 mg acetyl chloride under ice cooling, and stirring was continued at room temperature for two hours. The reaction mixture was washed with dilute hydrochloric acid and water in that order, the solvent was distilled off under reduced pressure, and the residue was purified by silica gel column chromatography, giving 150 mg of 1,3-bis[[3-(p-acetamidophenyl)-1-cycloheptylureido]methyl]benzene as amorphous solid.

- (i) ¹H-NMR (CDCl₃, δ ppm)
2.10 (6H, s), 4.08 (4H, s), 7.00 (4H, d)
- (ii) Mass (FAB) m/z 681 (M⁺ + 1)
- (iii) IR (cm⁻¹), 1666, 1650, 1614, 1556

Example 49

65

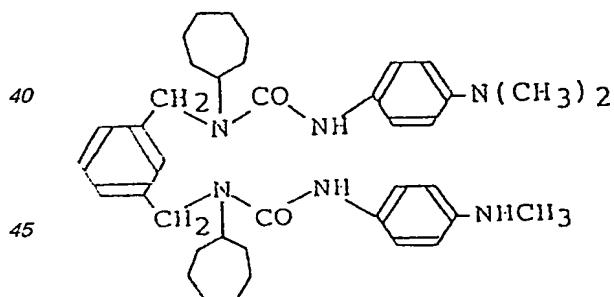


15 To a solution of 0.47 g 1,3-bis[[3-(*p*-aminophenyl)-1-cycloheptylureido]methyl]benzene (compound of Example 45) and 0.31 g of 37% formalin in 20 ml ethanol, was added 50 ml of platinum oxide, and the mixture was subjected to catalytic hydrogenation. After a predetermined volume of hydrogen gas was absorbed, the catalyst was filtered off, the solvents were distilled off under reduced pressure from the filtrate, and the residue was purified by silica gel column chromatography, giving 0.37 g of 1,3-bis[[1-cycloheptyl-3-(*p*-dimethylamino-phenyl)ureido]methyl]benzene as amorphous powder. This was treated with ethanolic hydrogen chloride, and the solid thus obtained was recrystallized from ethanol, affording 0.25 g of 1,3-bis[[1-cycloheptyl-3-(*p*-di-methylaminophenyl)ureido]methyl]benzene dihydrochloride.

- (i) M.p. 168–170°C
 (ii) Mass (FAB) m/z 653 ($M^+ + 1$)
 (iii) Elemental analysis (C₄₀H₅₈N₆O₂Cl₂)

| | | C | H | N |
|----|------------|-------|------|-------|
| 30 | Calcd. (%) | 66.19 | 8.05 | 11.58 |
| | Found (%) | 66.21 | 7.87 | 11.41 |

Example 50

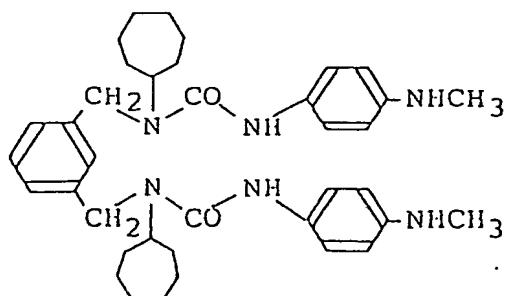


To a solution of 1 g 1,3-bis[[3-(*p*-aminophenyl)-1-cycloheptylureido]methyl]benzene (compound of Example 45) and 0.29 g of 35% formalin in 50 ml ethanol, was added 100 ml of platinum oxide, and the mixture was subjected to catalytic hydrogenation. After the absorption of hydrogen gas ceased, the catalyst was filtered off, the solvents were distilled off under reduced pressure from the filtrate, and the residue was purified by silica gel column chromatography, giving 0.19 g of 1-[[1-cycloheptyl-3-(*p*-dimethylaminophenyl)ureido]methyl]-3-[[1-cycloheptyl-3-(*p*-methylaminophenyl)ureido]methyl]benzene as amorphous powder.

- (i) $^1\text{H-NMR}$ (CDCl_3 , δ ppm)
 2.74 (3H, s), 2.84 (6H, s), 4.46 (4H, s)
 (ii) Mass (FAB) m/z 638 (M^+)
 (iii) IR (cm^{-1}), 1648, 1520, 1320, 1240

The following two compounds were prepared in much the same manner as in Example 50.

Example 51



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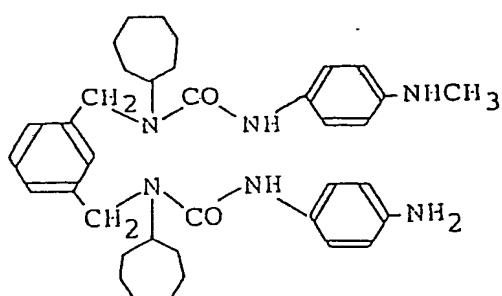
1,3-Bis[[1-cycloheptyl-3-(p-methylaminophenyl)ureido]-methyl]benzene

25

- (i) $^1\text{H-NMR}$ (CDCl_3 , δ ppm)
2.76 (6H, s), 4.46 (4H, s), 6.46 (4H, d)
- (ii) Mass (FAB) m/z 624 (M^+)
- (iii) IR (cm^{-1}), 1648, 1522, 1488, 1464

30

Example 52



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1-[[3-(p-Aminophenyl)-1-cycloheptylureido]methyl]-3-[[1-cycloheptyl-3-(p-methylaminophenyl)ureido]-methyl]benzene

50

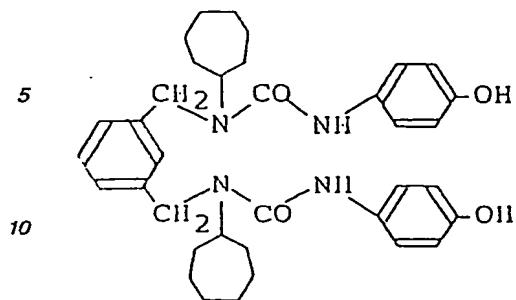
- (i) $^1\text{H-NMR}$ (CDCl_3 , δ ppm)
2.76 (3H, s), 4.48 (4H, s), 5.92 (2H, s)
- (ii) Mass (FAB) 610 (M^+)
- (iii) IR (cm^{-1}), 1648, 1520, 1238

55

Example 53

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65



15 A mixture of 2 g 1,3-bis[[3-(p-acetoxyphenyl)-1-cycloheptylureido]methyl]benzene (compound of Example 44), 30 ml ethanol and 30 ml of 5% aqueous sodium carbonate solution was heated under reflux for ten minutes. After distilling off the ethanol under reduced pressure, water was added to the residue, and the resulting mixture was acidified by addition of concentrated hydrochloric acid under ice cooling. The solid which separated out was collected by filtration and recrystallized from methanol, giving 1 g of 1,3-bis[[1-cycloheptyl-3-(p-hydroxyphenyl)ureido]methyl]benzene.

(i) M.p. 230-231°C

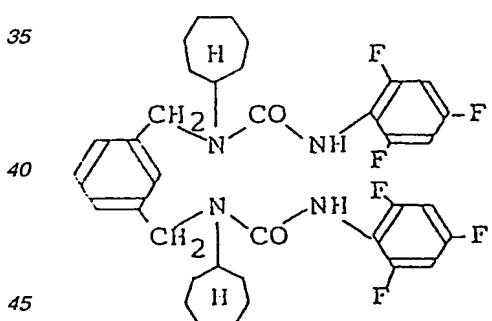
(ii) Mass (FAB) m/z 599 ($M^+ + 1$)

(iii) Elemental analysis ($C_{36}H_{46}N_4O_4$)

25

| | C | H | N |
|------------|-------|------|------|
| Calcd. (%) | 72.21 | 7.74 | 9.36 |
| Found (%) | 72.18 | 7.72 | 9.23 |

30 Example 54



50 A mixture of 0.82 g N,N'-dicycloheptyl-m-xylylenediamine, 1.26 g phenyl 2,4,6-trifluorophenylcarbamate and 50 ml toluene was heated under reflux for one hour. After cooling, the reaction mixture was washed twice with 50 ml of 1N-NaOH solution and then with sodium chloride solution, and dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure from the dried solution, and the residue was recrystallized from acetone, giving 1.02 g of 1,3-bis[[1-cycloheptyl-3-(2,4,6-trifluorophenyl)ureido]methyl]benzene.

(i) M.p. 107-108°C

(ii) Mass (FAB) m/z 674 (M^+)

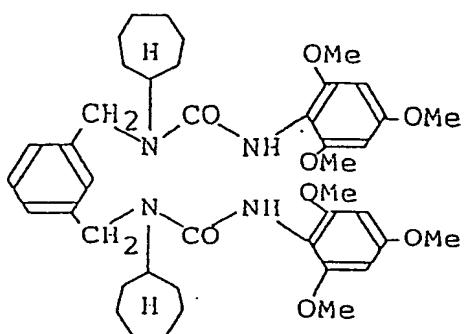
55 (iii) Elemental analysis ($C_{36}H_{40}N_4F_6O_2$)

| | C | H | N |
|------------|-------|------|------|
| Calcd. (%) | 64.08 | 5.98 | 8.30 |
| Found (%) | 63.88 | 5.95 | 8.29 |

5 The following compound was prepared in much the same manner as in Example 29.

Example 54

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1,3-Bis[[3-(2 , 4 , 6-trimethoxyphenyl)-1-cycloheptylureido]-methyl]benzene

35

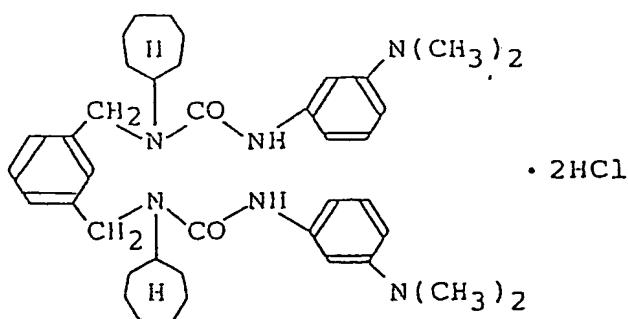
- (i) M.p. 133-134.5°C
- (ii) Mass (FAB) m/z 747 (M⁺)
- (iii) Elemental analysis (C₄₂H₅₈N₄O₈)

| | C | H | N |
|------------|-------|------|------|
| Calcd. (%) | 67.54 | 7.83 | 7.50 |
| Found (%) | 67.07 | 7.84 | 7.33 |

40

Example 56

45



50

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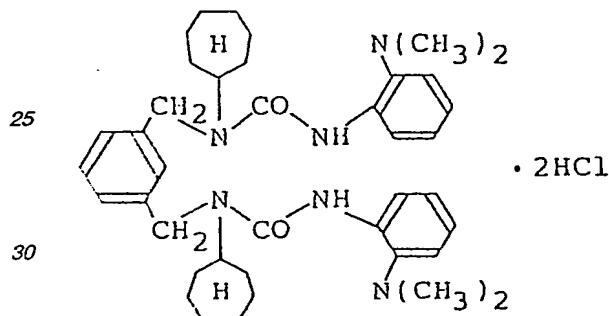
65

To a mixture of 0.50 g 1,3-bis[[3-(m-aminophenyl)-1-cycloheptylureido]methyl]benzene (compound of Example 46), 0.17 ml of 35% formalin, 30 ml acetonitrile and 100 ml chloroform, was added with stirring 0.11 g sodium cyanoborohydride at room temperature, and stirring was continued for 20 hours. Sodium cyanoborohydride (0.11 g) and 35% formalin (0.17 ml) were further added, and the mixture was stirred for two hours. Acetic acid (1ml) was then added, and stirring was continued for an additional 30 minutes. The resulting solution was washed with 50 ml of 1N-KOH solution, the aqueous layer was extracted thrice with 100 ml chloroform, and the combined organic solution was washed with aqueous sodium chloride and dried over anhydrous sodium sulfate. The solvents were distilled off under reduced pressure from the dried solution, and the residue was purified by silica gel column chromatography, followed by treatment with ethanolic hydrogen chloride. Distilling off the solvent gave 0.25 g of 1,3-bis[[1-cycloheptyl-3-(m-dimethylaminophenyl)ureido]methyl]benzene dihydrochloride as amorphous powder.

- (i) $^1\text{H-NMR}$ (DMSO- d_6 , δ ppm)
 3.13 (12H, s), 4.59 (4H, s)
 (ii) Mass (FAB) 653 ($M^+ + 1$)
 (iii) IR (cm^{-1}), 2936, 1654, 1540, 1464

Example 57

20



35

To a mixture of 0.6 g 1,3-bis[[3-(o-aminophenyl)-1-cycloheptylureido]methyl]benzene (compound of Example 47), 0.43 ml of 35% formalin, 50 ml acetonitrile and 50 ml benzene, was added with stirring 0.12 g sodium cyanoborohydride at room temperature, and stirring was continued for two hours. Sodium cyanoborohydride (0.12 g) and 35 formalin (0.43 ml) were further added, and the mixture was stirred for two hours. Acetic acid (1ml) was then added, and stirring was continued for an additional 30 minutes. The solvents were distilled off from the reaction mixture, and 50 ml of 1N-KOH solution was added, followed by extraction with 50 ml chloroform three times. The extract was washed with saturated aqueous sodium chloride and dried over anhydrous potassium carbonate. The solvent was distilled off under reduced pressure from the dried solution, and the residue was purified by silica gel column chromatography and then recrystallized from acetone, giving 0.16 g of 1,3-bis[[1-cycloheptyl-3-(o-dimethylaminophenyl)ureido]methyl]benzene dihydrochloride.

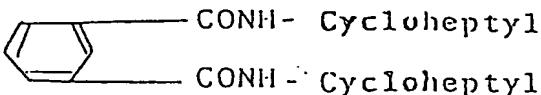
- (i) M.p. 159-160°C
 (ii) Mass (FAB) m/z 653 (M^+)
 (iii) Elemental analysis ($C_{40}\text{H}_{56}\text{N}_6\text{O}_2$)

| | C | H | N |
|------------|--------|------|-------|
| Calcd. (%) | 73.58 | 8.64 | 12.87 |
| Found (%) | 73.42. | 8.75 | 12.76 |

Reference Example 10

60

65



5

20.8 g of cycloheptylamine and 20.25 g of triethylamine were dissolved in 500 ml of methylenechloride, and then 17.0 g of iso-phthaloyl chloride was added thereto. The mixture was stirred at room temperature for 2 hours, 500 ml of water was added, then conc. HCl was added thereto while stirring. Precipitated material was collected by filtration, washed with methylene chloride and water successively, and dried giving 28.7 g of N,N'-dicycloheptylisophthalamide.

10

mp. 285-286°C

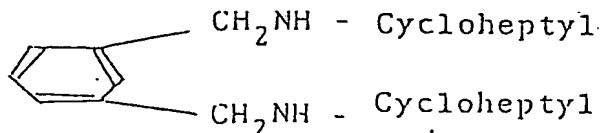
15

IR (cm⁻¹): 3264, 1648, 1632, 1560

Mass (m/z): 356 (M⁺)

Reference Example 11 (Starting material in Example 1 and other Examples)

20



25

24.3 g of N,N'-dicycloheptylisophthalamide (obtained in Reference Example 10) was suspended in 500 ml of toluene, and 96 ml of toluene solution (70%) containing bis(2-methoxyethoxy)aluminum sodium hydride was added thereto dropwise while stirring at room temperature. The mixture was refluxed for 3 hours, and 400 ml of 2.5N aqueous sodium hydroxide was added thereto portionwise. The toluene layer was separated and collected, washed with saturated aqueous NaCl, and dried. The solution was removed by distillation, giving 22.3 g of N,N-dicycloheptyl-m-xylenediamine.

30

¹H-NMR (CDCl₃, δ ppm): 3.74 (4H, s), 7.08-7.36 (4H, m),

35

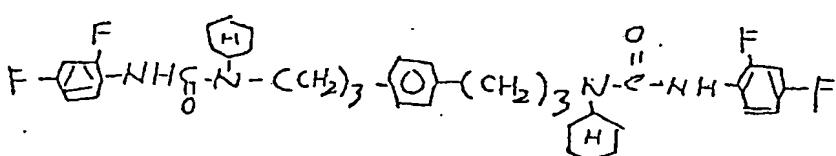
IR (cm⁻¹): 2936, 2860, 1462, 1114

Mass (FAB) m/z 329 (M⁺+1)

40

Example 58

45



50

1,4-bis[(1-cyclohexyl-3-(2,4-difluorophenyl)ureido)-propyl]benzene

55

60

The above compound was prepared in much the same manner as in Example 14.

(i) M.p. 76-78°C

(ii) ¹H-NMR (CDCl₃, δ ppm)

2.14 (4H, t), 3.20 (4H, t), 6.26 (2H, d)

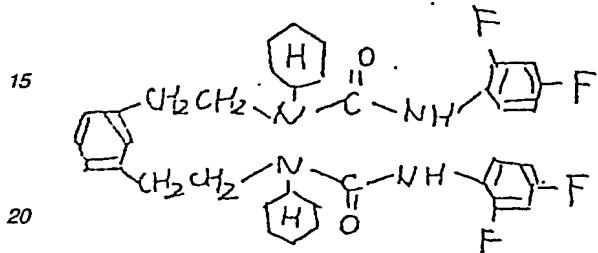
65

(iii) Elemental analysis ($C_{38}H_{46}N_4O_2F_4$)

| | C | H | N |
|--------------|-------|------|------|
| 5 Calcd. (%) | 68.45 | 6.95 | 8.40 |
| 5 Found (%) | 68.66 | 7.13 | 8.22 |

Example 59

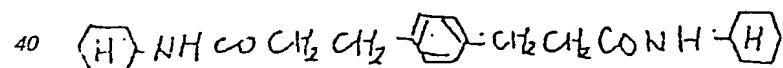
10



25 1,3-bis[(1-cyclohexyl-3-(2,4-difluorophenyl)ureido)ethyl]benzene

30 The above compound was prepared in much the same manner as in Example 1.

- (i) 1H -NMR ($CDCl_3$, δ ppm)
2.88 (4H, t), 3.32 (4H, t), 6.38 (2H, d)
- (ii) IR (cm^{-1}) 2944, 1654, 1522, 1432

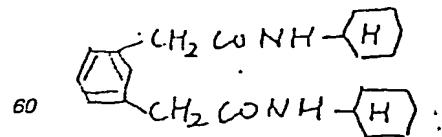
35 Reference Example 12

45 To a solution of 4.9 g of cyclohexylamine and 5.4 g of triethylamine in 100 ml of methylenechloride, was added 5.8 g of 1,4-phenylenedipropionyl chloride under ice cooling with stirring. Stirring was continued for 3 hours at room temperature, and 500 ml of water was added to the reaction solution. Conc. HCl was added to the mixture until the aqueous layer became weakly acidic. The solid material precipitated was collected by filtration, washed with methylenechloride and water in that order, and dried, giving 7.4 g of N,N'-dicyclohexyl-1,4-phenylenedipropionamide.

- 50
- (i) M.p. 267-269°C
 - (ii) IR (cm^{-1}) 3312, 1642, 1548

Reference Example 13

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N,N-dicyclohexyl-1,3-phenylenediacetamide

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- (i) M.p. 221-222°C
(ii) IR (cm^{-1}) 3304, 2944, 1646, 1550

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Reference Example 14 (Starting material for Example 58)

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1.5 g of N,N'-dicyclohexyl-1,4-phenylenedipropionamide was added to 20 ml of dry tetrahydrofuran, and after adding thereto dropwise 2.4 ml of boran dimethyl sulfide complex under ice cooling, the mixture was refluxed under heating for 4 hours. After adding to the mixture 0.33 ml of methanol under ice cooling and stirring the mixture for 30 minutes at room temperature, 2 ml of conc.-HCl was added to the mixture under ice cooling. The mixture was refluxed for 30 minutes. The reaction solution was ice-cooled, and the solid material precipitated was collected by filtration and washed with ether. The solid material thus obtained was dissolved in chloroform, and the solution was alkalified with aqueous NaOH. The chloroform layer was dried, and the solvent was distilled away under reduced pressure, giving 1.3 g of N,N'-dicyclohexyl-1,4-phenylenedipropylamine.

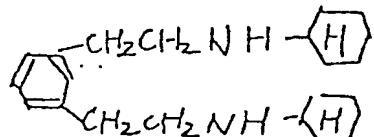
25

- (i) $^1\text{H-NMR}$ (CDCl_3 , δ ppm)
7.12 (4H, s)
(ii) IR (cm^{-1}) 2936, 2856, 1516, 1452
(iii) Mass spectrum (EI) m/z 356 (M^+)

30

Reference Example 15 (Starting material for Example 59)

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N,N-dicyclohexyl-1,3-phenylenedietylamine

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The above compound was prepared in much the same manner as in Reference Example 14.

- (i) $^1\text{H-NMR}$ (CDCl_3 , δ ppm)
2.90 (8H, t)
(ii) IR (cm^{-1}) 2936, 2856, 1452, 1130

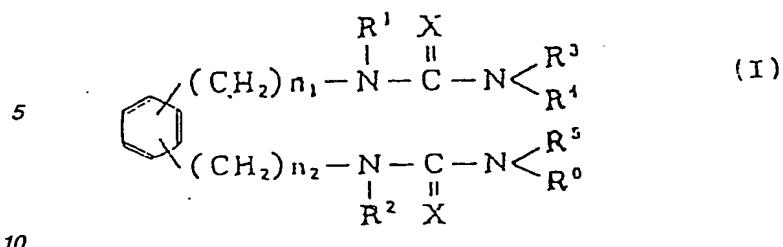
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Claims

A compound of formula (I) or a salt thereof:

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15 wherein R¹ and R² are the same or different and selected from alkyl and cycloalkyl groups and C₁-C₅ alkyl groups substituted by cycloalkyl; R³, R⁴, R⁵ and R⁶ are the same or different and selected from a hydrogen atom and C₁-C₅ alkyl, cycloalkyl, aralkyl, pyridyl, and phenyl groups; X is an oxygen or sulfur atom; and n₁ and n₂ are the same or different integers of 1 to 6.

2. A compound according to claim 1 wherein R¹ and R² are cycloalkyl groups; R³ and R⁵ are the same or different phenyl groups; R⁴ and R⁶ are the same or different and selected from a hydrogen atom and C₁-C₅ alkyl, cycloalkyl, aralkyl, pyridyl, and phenyl groups; n₁ and n₂ are integers of 1 to 3.

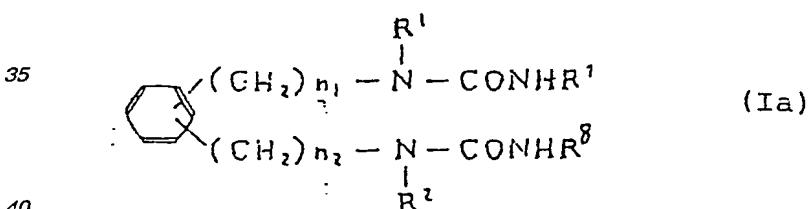
20 3. A compound according to claim 1 or 2 wherein at least one said phenyl groups is substituted, preferably by one or more substituents selected from C₁-C₅ alkyl, halogeno-(C₁-C₅ alkyl), halogen, nitro, amino, mono- and di-(C₁-C₅ alkyl) amino, (C₁-C₅ acyl)amino, hydroxyl, C₁-C₅ alkoxy and C₂-C₅ acyloxy.

4. A compound according to claim 1 which 1,3-bis[(1-cycloheptyl-3-(2,4-difluorophenyl)-ureido)methyl]benzene or a salt thereof.

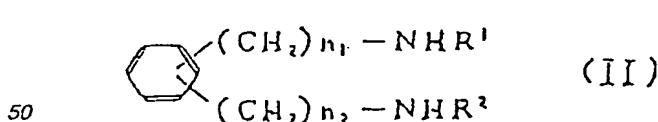
25 5. A compound according to claim 1 which is 1,3-bis[(1-cycloheptyl-3-(p-dimethylaminophenyl)-ureido)methyl]benzene or salt thereof.

6. A medical composition containing as an active component a compound or pharmaceutically acceptable salt according to any of claims 1 to 5.

7. A process for producing a compound (Ia)

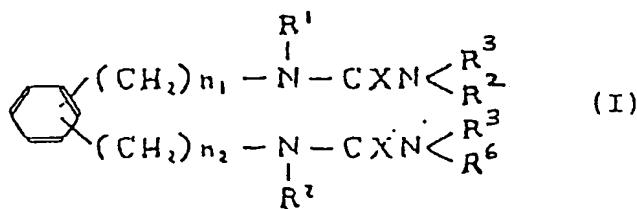


which comprises reacting compound (II)



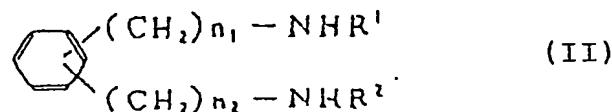
55 with compound(s) (III)
 R^7NCX (and/or R^8NCX) (III)
 and optionally converting the product to or from salt form, wherein R^1 , R^2 , X , n_1 and n_2 are as defined in
 claim 1, 2 or 3 and R^7 and R^8 are as defined for R^3 to R^6 in claim 1, 2 or 3.

8. A process for producing a compound (I)



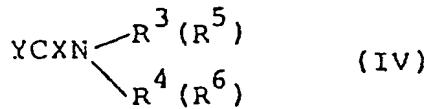
which comprises reacting compound (II)

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with compound(s) (IV)

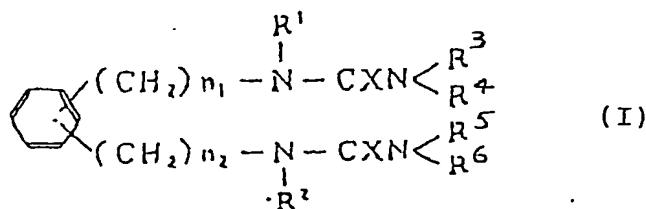
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and optionally converting the product to or from salt form, wherein R¹ to R⁶, X, n₁ and n₂ are as defined in claim 1, 2 or 3 and Y is halogen.

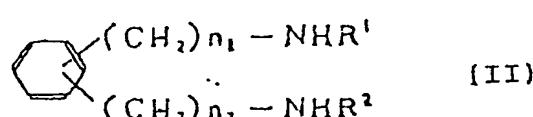
9. A process for producing a compound (I)

35



which comprises reacting compound (II),

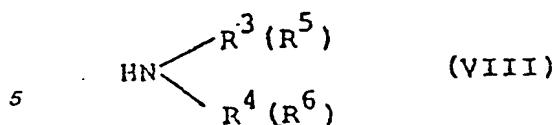
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Y-CXO-R⁹, and compound(s) (VIII)

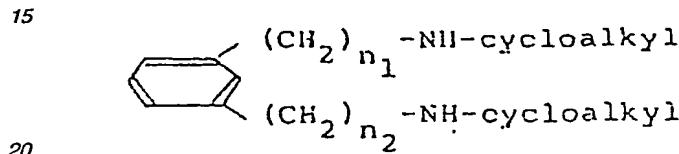
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10 and optionally converting the product to or from salt form, wherein R¹ to R⁶, X, n₁ and n₂ are as defined in claim 1, 2 or 3 and R⁹ represents C₁-C₅ alkyl or a phenyl group.

10. An intermediate compound of the following formula:



wherein n_1 and n_2 are the same or different integers of 1 to 6.

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| DOCUMENTS CONSIDERED TO BE RELEVANT | | | EP 89300380.6 |
|--|---|-------------------|---|
| Category | Citation of document with indication, where appropriate, of relevant passages | Relevant to claim | CLASSIFICATION OF THE APPLICATION (Int. Cl.4) |
| A | EP - B1 - 0 000 376 (NIHON TOKUSHU NOYAKU SEIZO) * Claims 1,2 * -- | 1,7 | C 07 C 127/19 C 07 C 127/17 C 07 C 157/09 C 07 C 157/07 C 07 C 87/455 A 61 K 31/17 |
| A | EP - A2 - 0 072 528 (BAYER) * Claims 1,3,4 * -- | 1,7,10 | |
| A | US - A - 4 460 602 (BRIAN L. BUCKWALTER et al.) * Abstract * -- | 1,6 | |
| X | DE - B - 1 942 877 (SHOWA DENKO) * Table; compound 12 * -- | 10 | |
| X | CHEMICAL ABSTRACTS, vol. 74, no. 23, June 7, 1971, Columbus, Ohio, USA BERGMANN, ERNST D et al. "Synthesis and properties of some phosphorusaziridinyl compounds" page 441, abstract no. 125 293g in connexion with Chem. Abstr. Collective Index, vol. 66-75, page 7290 F, C ₁₈ H ₂₈ N ₂ , last compound & J. Polym. Sci., Part C, 1970, No. 31, 375-97 ----- | 10 | TECHNICAL FIELDS SEARCHED (Int. Cl.4) C 07 C 127/00 C 07 C 157/00 C 07 C 87/00 |
| The present search report has been drawn up for all claims | | | |
| Place of search | Date of completion of the search | Examiner | |
| VIENNA | 03-04-1989 | REIF | |
| CATEGORY OF CITED DOCUMENTS | T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document | | |